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Title: The Art of Electrophysiological Modeling

Author(s): John C. Mosher, Ph.D.

Submitted to: Image Analysis and Understanding Data from Scientific Analysis
CNLS Los Alamos Imaging Workshop
2-6 December 2002

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Los Alamos NATIONAL LABORATORY

The Art of Electrophysiological Modeling

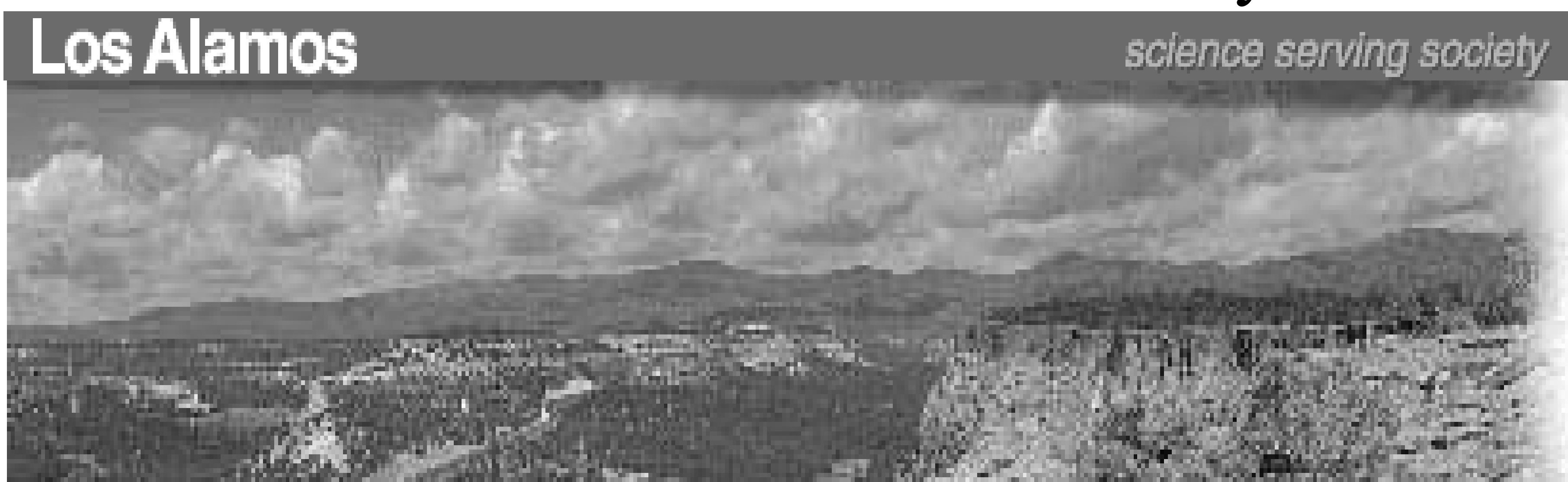
John C. Mosher, Los Alamos National Laboratory

Magnetoencephalography (MEG) measures the extremely weak quasistatic magnetic field outside the scalp generated by neural activity within the brain; electroencephalography (EEG) measures the scalp potentials from the same activity. The forward problem is the calculation of the external fields given an elemental source within the brain, for which the solution is analytic for spheres and more generally solved using numerical methods for tessellated shapes. Because the fields are nearly static, the forward models are specializations of the Newtonian potential measured from a distance, and therefore the inverse solution is ambiguous, without the imposition of strong models. In practice, the fields are measured at a few hundred sites about the upper hemisphere of the head, in the presence of substantial environmental and biological noise, and sampling rates and filtering protocols restrict the bandwidth to about 100 Hz, recorded on the order of ten minutes. Magnetic resonance images are used as anatomical basis sets on which to project most of the present day functional solutions. We review the basics of the acquisition systems and forward modeling, then focus on the inverse modeling approaches used to process these large spatiotemporal data matrices.

The Art of Electrophysiological Modeling

John C. Mosher, Ph.D.

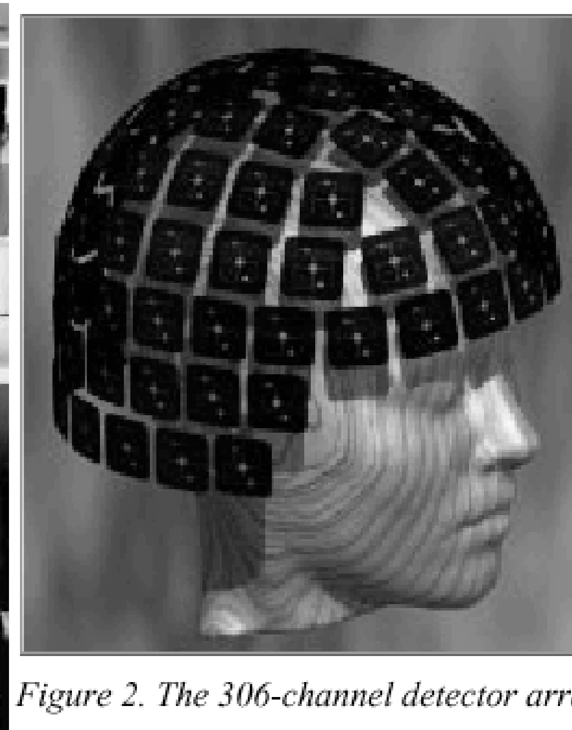
Weapons Design Technology Group
Los Alamos National Laboratory

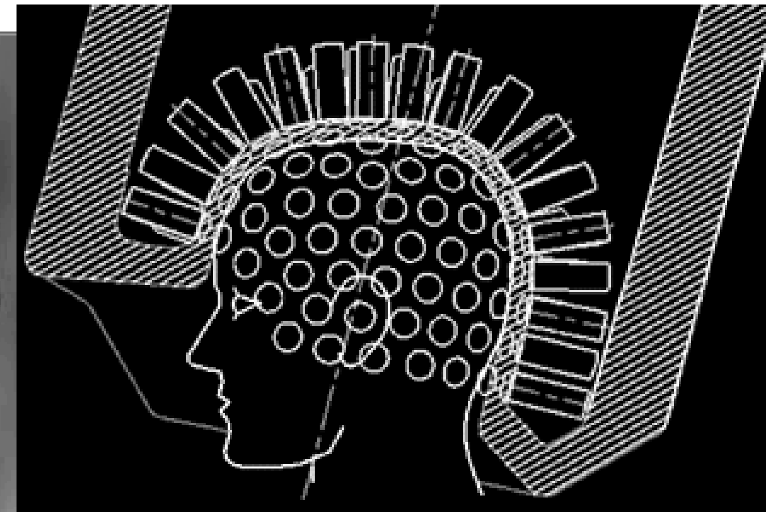


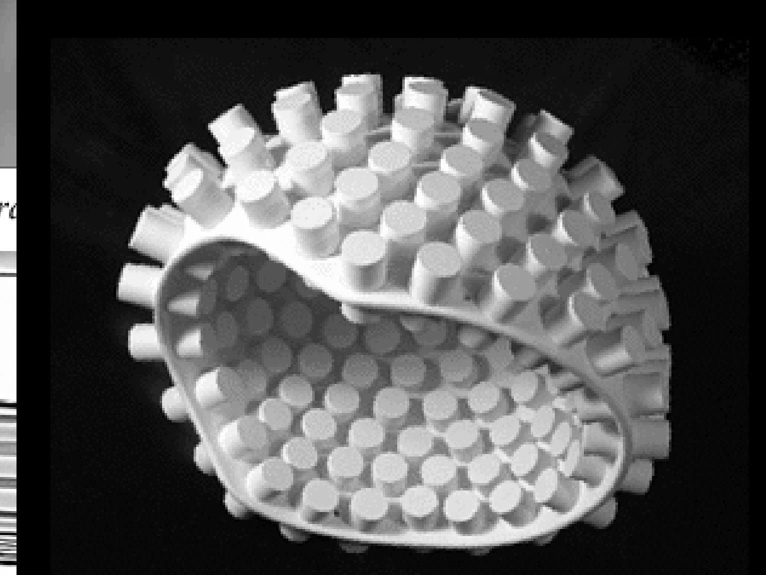
What is Magnetoencephalography?

- The magnetic field generated by neural activity
  - Measured in femtoTeslas, one billion times weaker than Earth's magnetic field.
- Requires SQUID technology
- The magnetic equivalent to electroencephalography
  - Complementary, "curl" vs. "divergence" of vector potential

Magnetoencephalography: Commercial Arrays

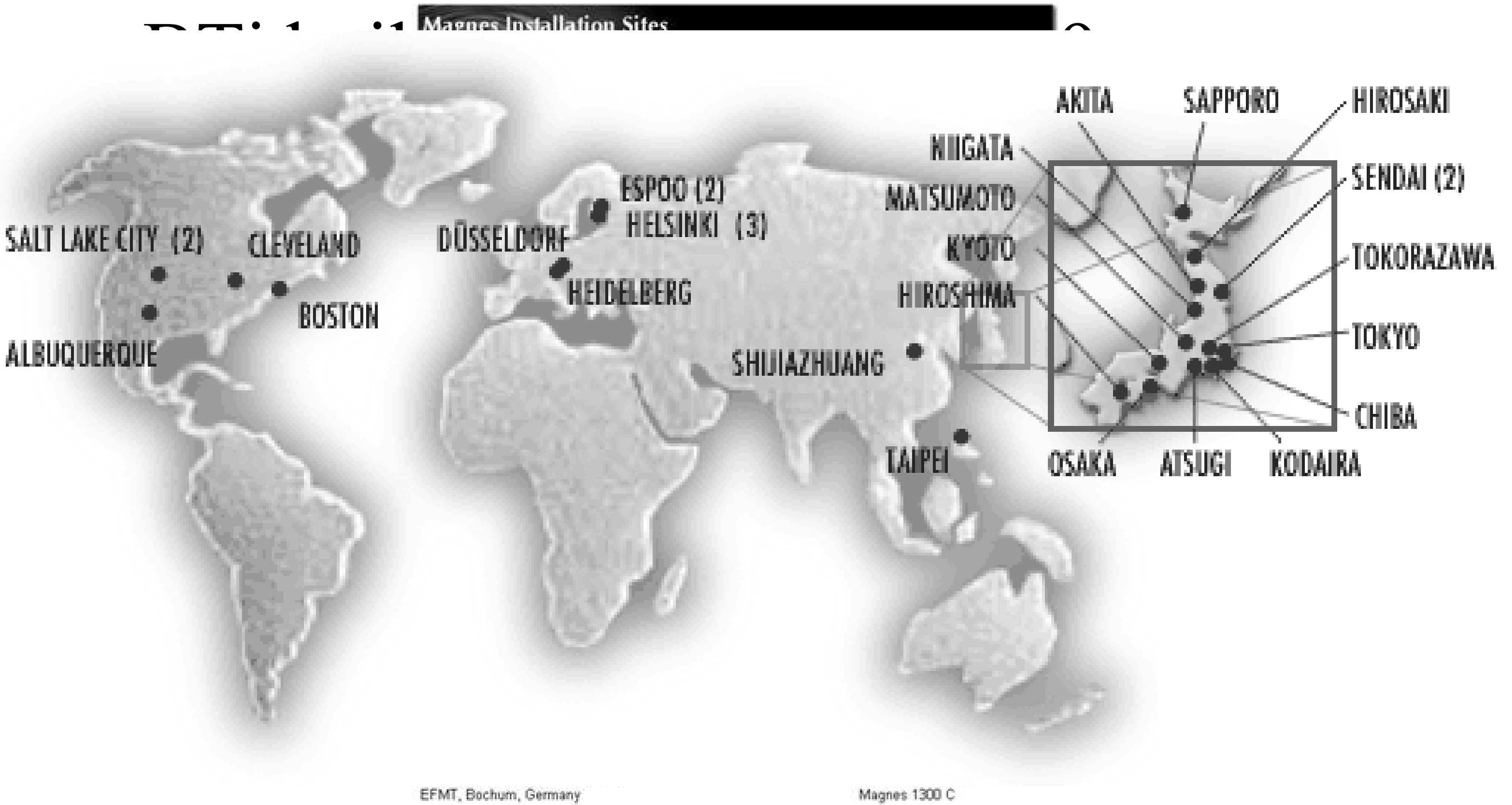






CTF.com, Neuromag.com,
4DNeuroimaging.com

Large Array MEG Machines



Huntington Memorial Research Inst.

- CTF 68-Channel MEG, 64 Channel EEG Whole Head Arrays

Pasadena, CA

Laboratoire de Neurosciences Cognitives & Imagerie Cerebrale

- CTF 151-Channel MEG, axial gradiometers, 64-128 EEG,

Paris, France

Minnesota Brain Sciences Center

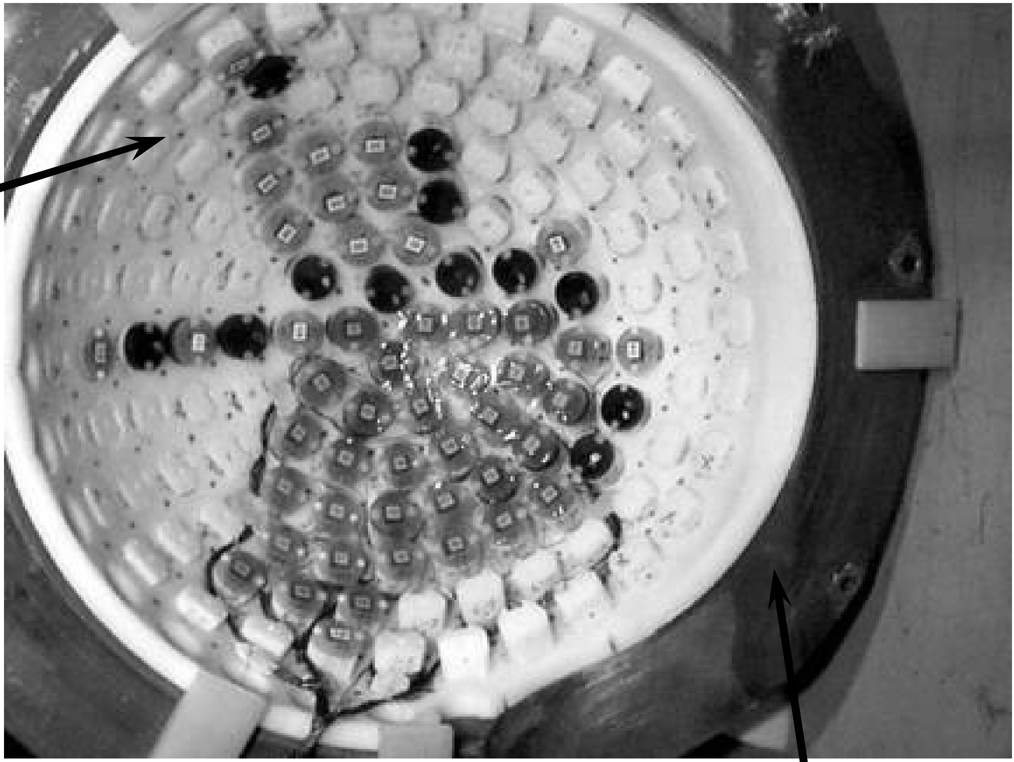
- 4-D Magnes 3600, 248 Channels MEG, 64 Channels EEG
- Axial gradiometers, 5cm baseline

LANL Superconducting Imaging Surface

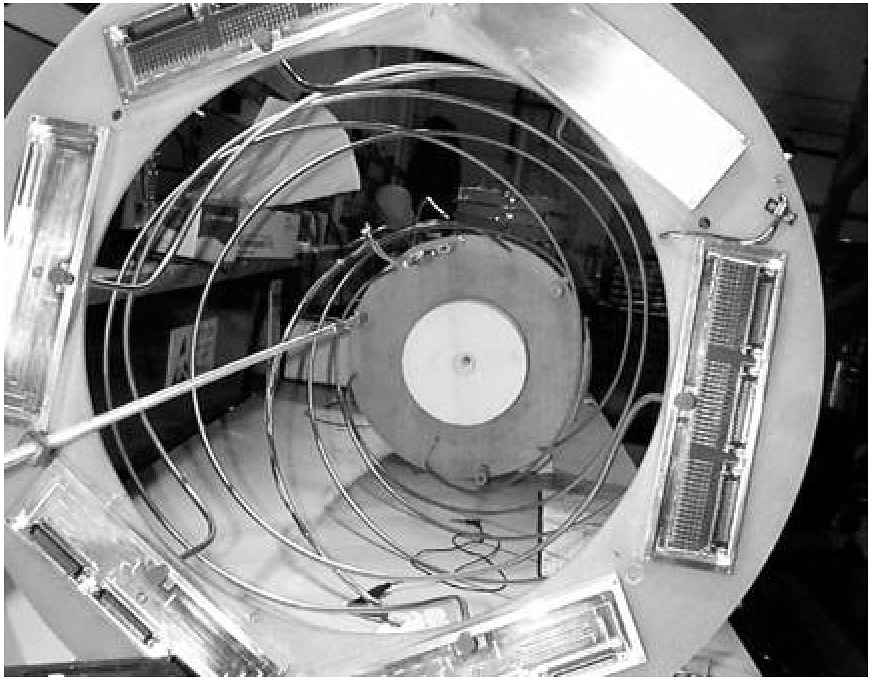
The LANL Whole-Head MEG System - version 3

SQUID array inside super-conducting imaging surface "helmet" (50 of 155 SQUIDs)

Corian®-like support and mounting structure. (DuPont/LANL Patent)

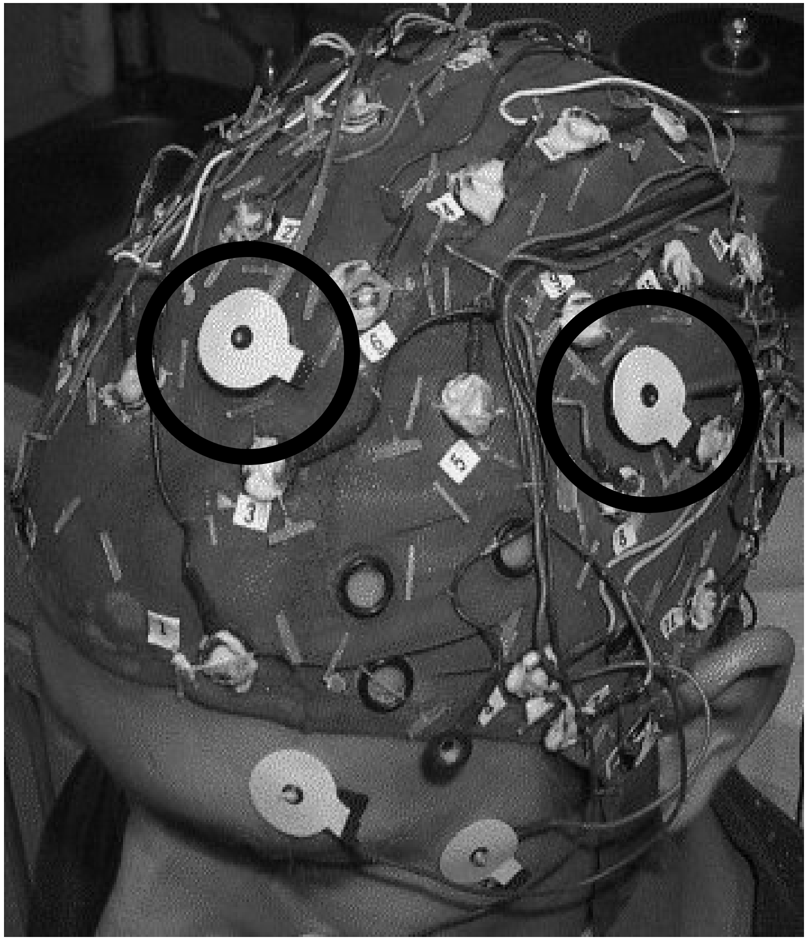


Lead Superconducting "helmet". (replacing Niobium)



The cryogenic column with new wire path design to improve cooling at ~4 Kelvins and SCSI connectors.

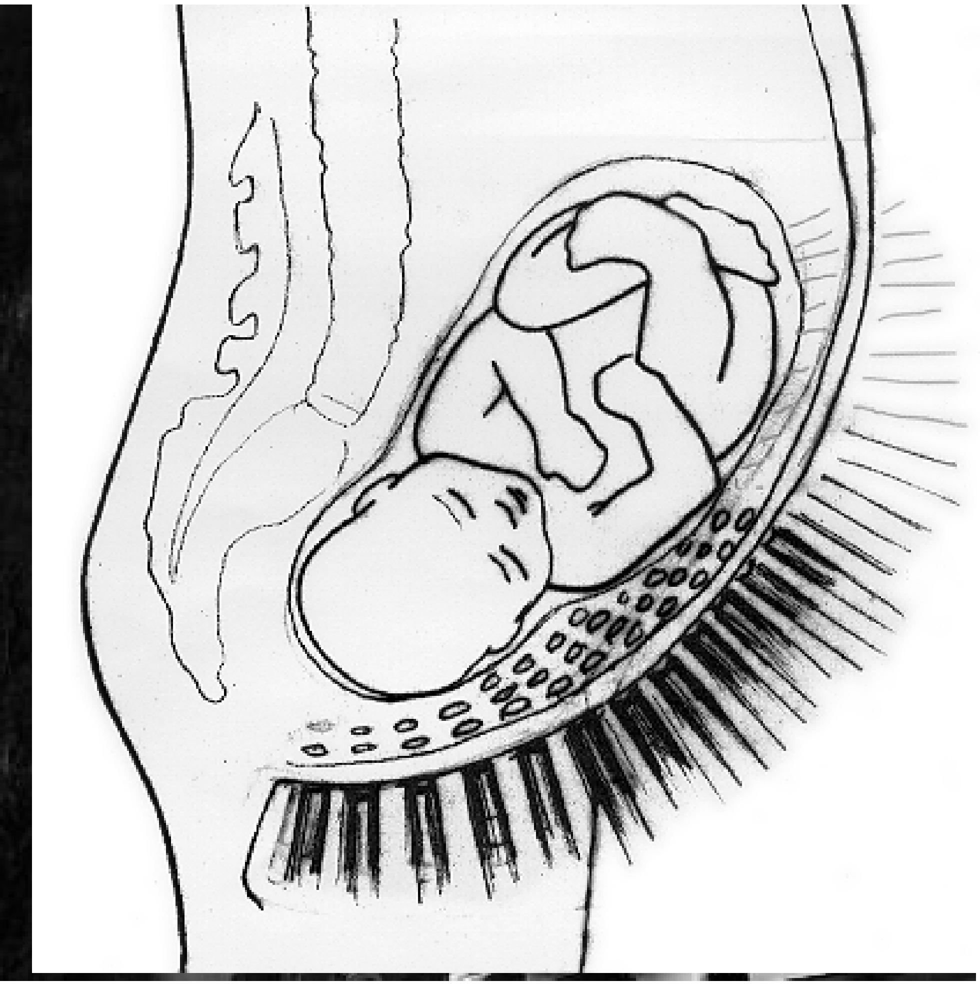
Combined EEG and MEG



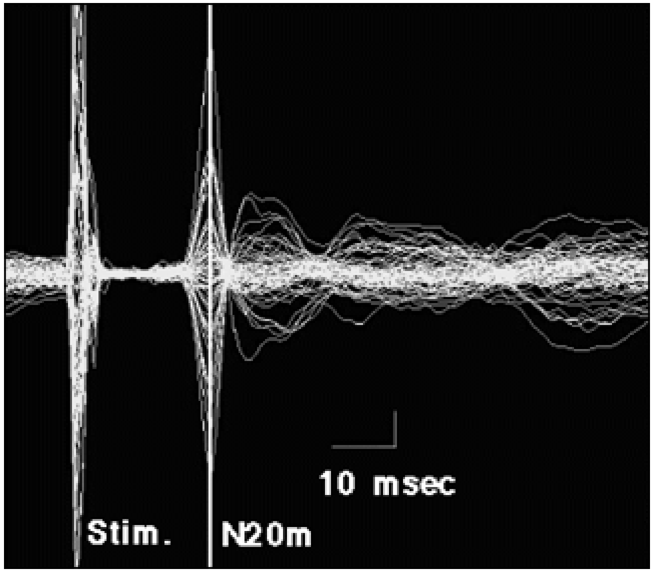
BrainStorm

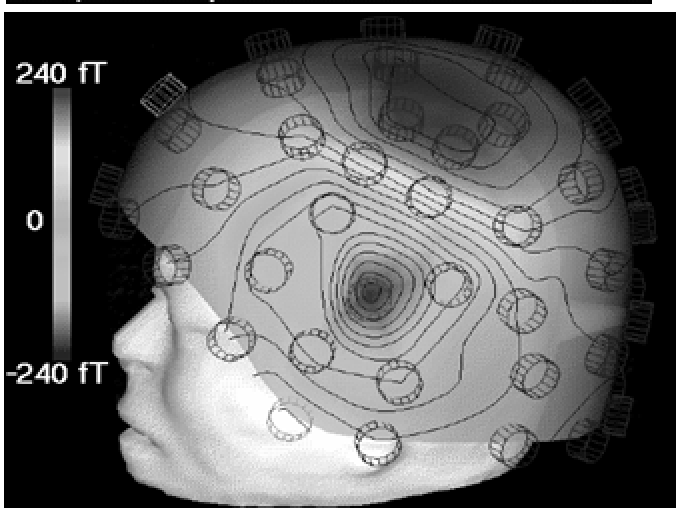
- Typically up to 64 channels over the head.
- MEG localization coils also added to locate head in array.
- Additional eye-blink channels.

Other Magnetic Field Arrays



Neuromagnetic Example

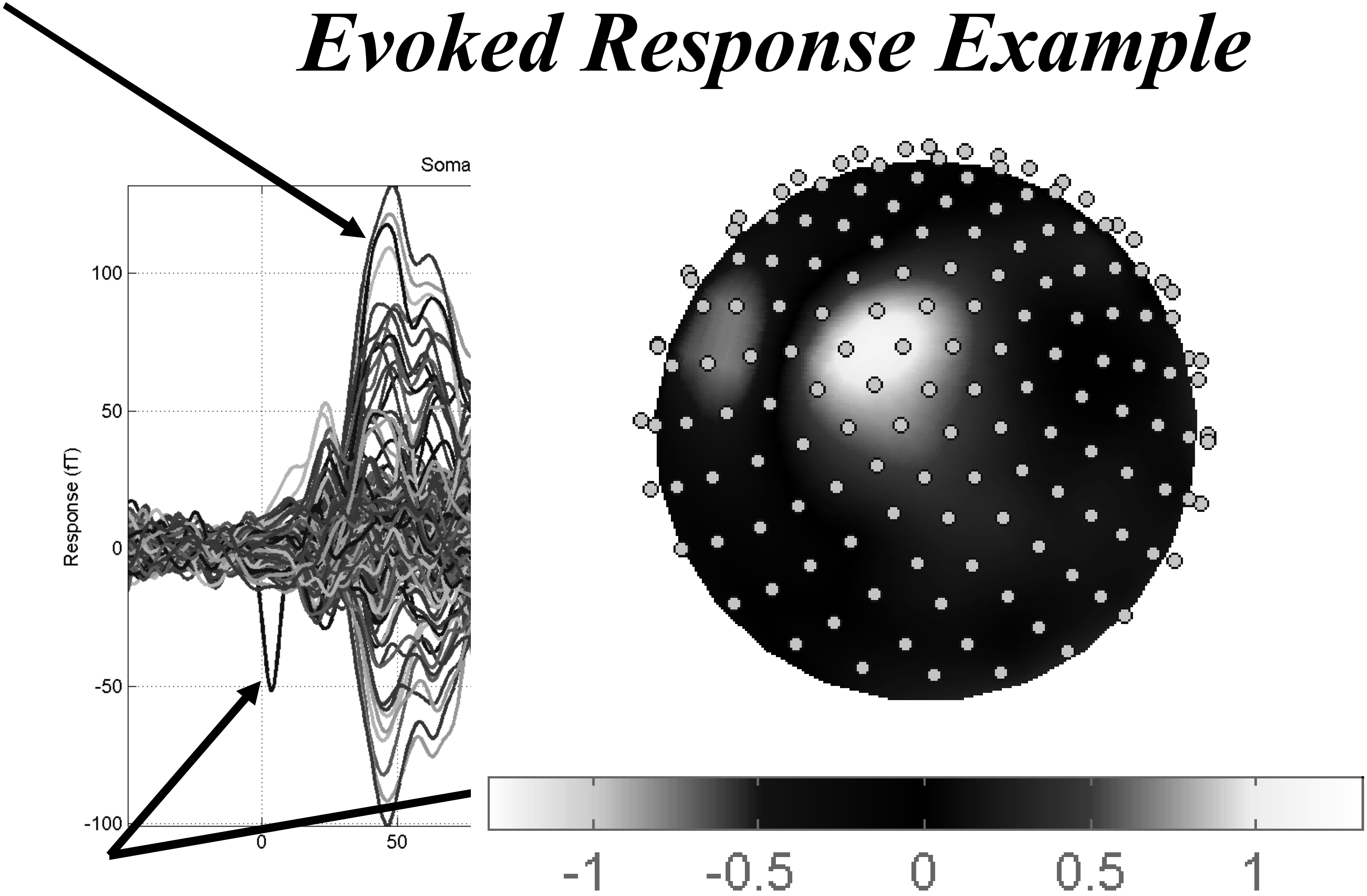




- **Temporal:** Averaged event-related signals - high temporal resolution monitoring of neural activation
- **Spatial:** Snap-shot topographic maps of external magnetic fields
- **Problem:** find the sources in space and time

Ctf.com

Evoked Response Example



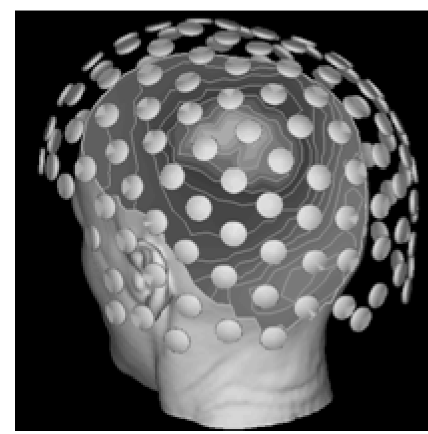
Outline

- "Imaging" vs. "Modeling" of data
- Similar Physical Sciences
- Forward Modeling
- Inverse Modeling
- Simulated and Experimental Results

Collaborators

- **University of Southern California**
  - Professor Richard Leahy, Director, Signal & Image Processing Institute
- **Cognitive Neuroscience & Brain Imaging Laboratory (CNRS), Paris**
  - Dr. Sylvain Baillet, BrainStorm
- **Biophysics Group, LANL**
- **Huntington Memorial, Pasadena**
- **MIND Institute (UNM, UMN, VA)**

USC
UNIVERSITY OF SOUTHERN CALIFORNIA



MIND

Tutorial Overview

IEEE Signal Processing Magazine, Nov 2001

Baillet, Mosher, Leahy

See also web site at University of Southern California: neuroimage.usc.edu.

Electromagnetic Brain Mapping

Sylvain Baillet, John C. Mosher, and Richard M. Leahy

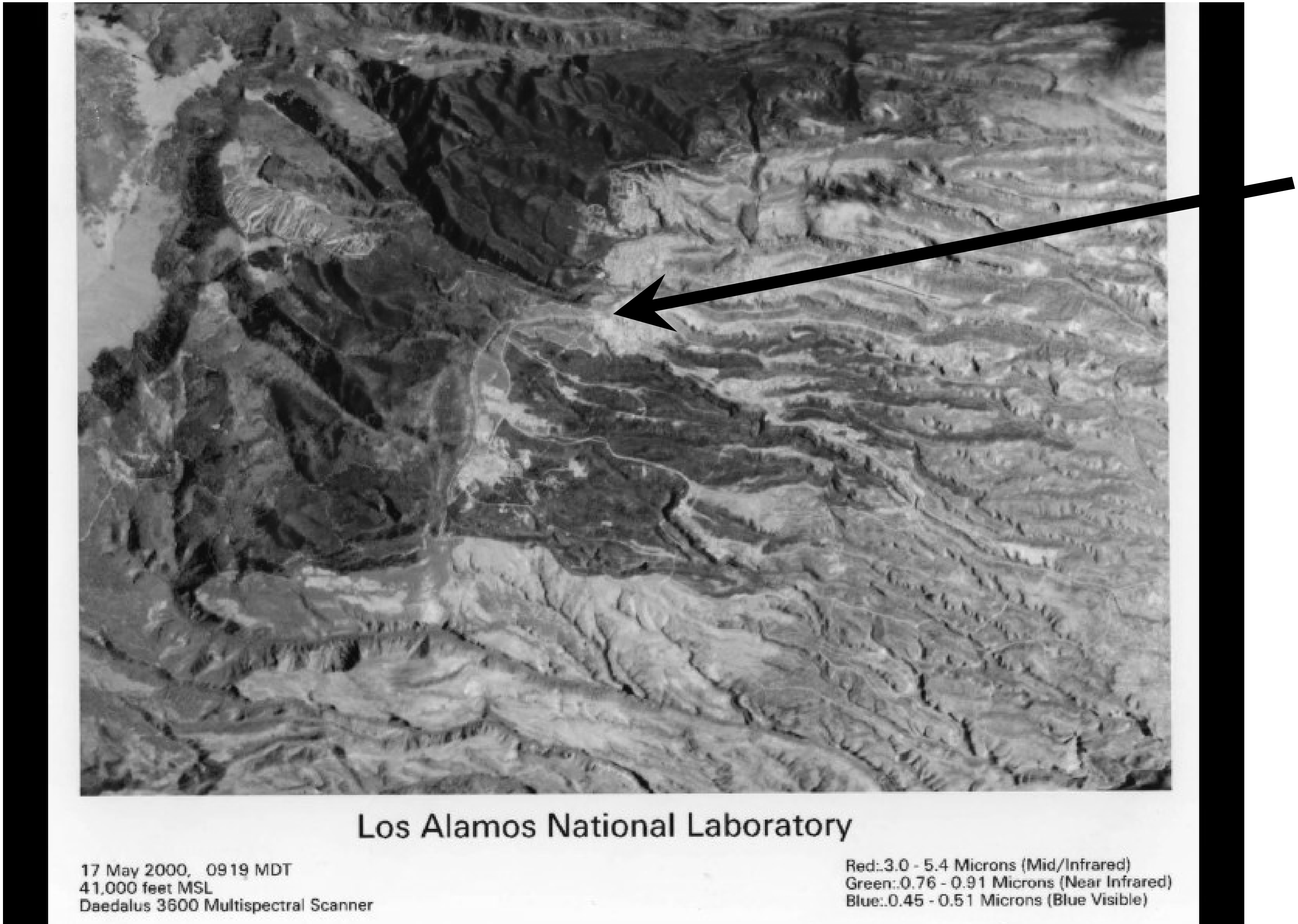
The past 15 years have seen tremendous advances in our ability to produce images of human brain function. Applications of functional brain imaging extend from improving our understanding of the basic mechanisms of cognitive processes to better characterization of pathologies that impair normal function. Magnetoencephalography (MEG) and electroencephalography (EEG) (MEG/EEG) localize neural electrical activity using noninvasive measurements of external electromagnetic signals. Among the available functional imaging techniques, MEG and EEG uniquely have temporal resolutions below 100 ms. This temporal precision allows us to explore the timing of basic neural processes at the level of cell assemblies. MEG/EEG source localization draws on a wide range of signal processing techniques including digital filtering, three-dimensional image analysis, array signal processing,

Summer 2000, Los Alamos Fire!

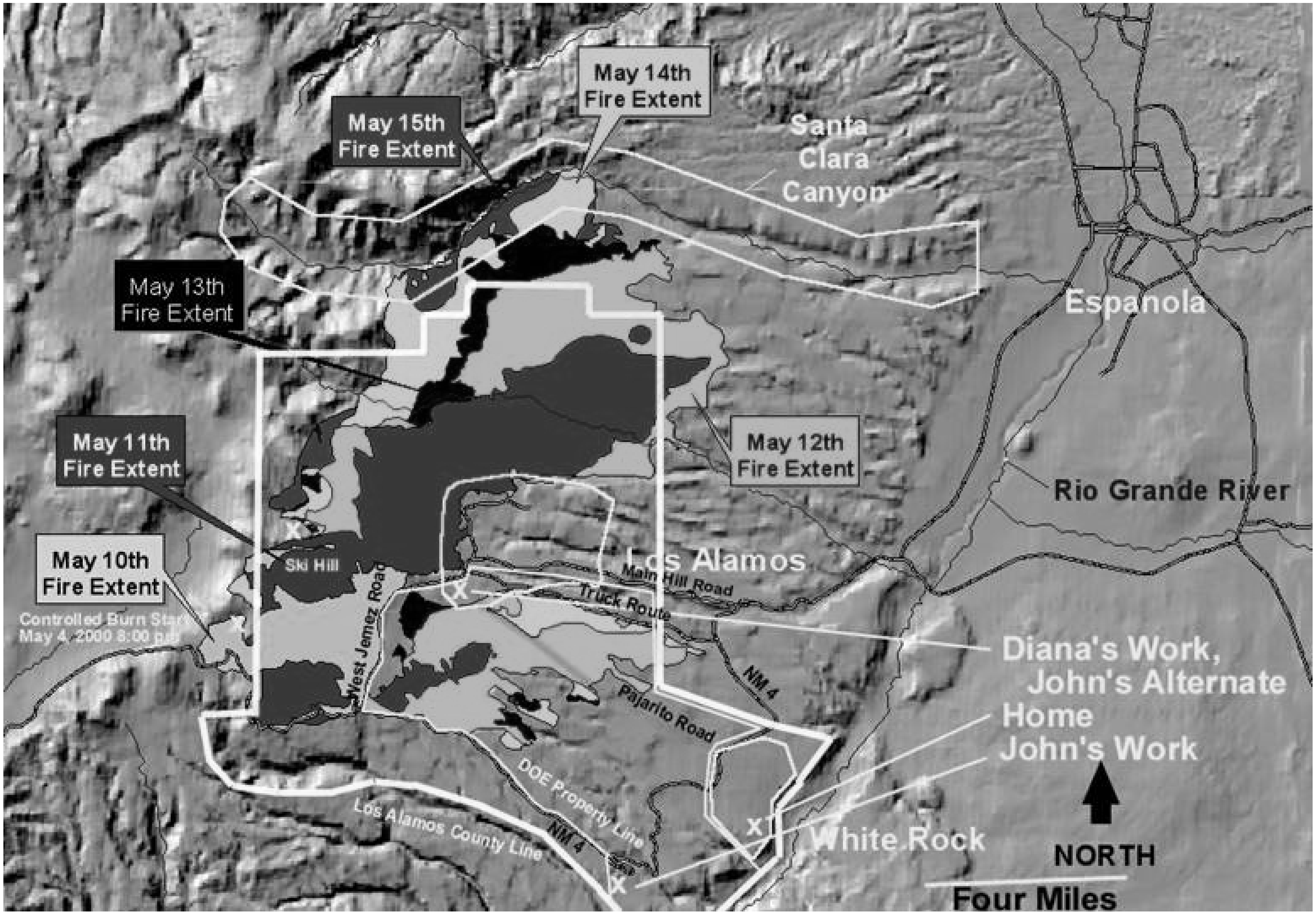
We're from the Government, and we're here to help you!

You are here

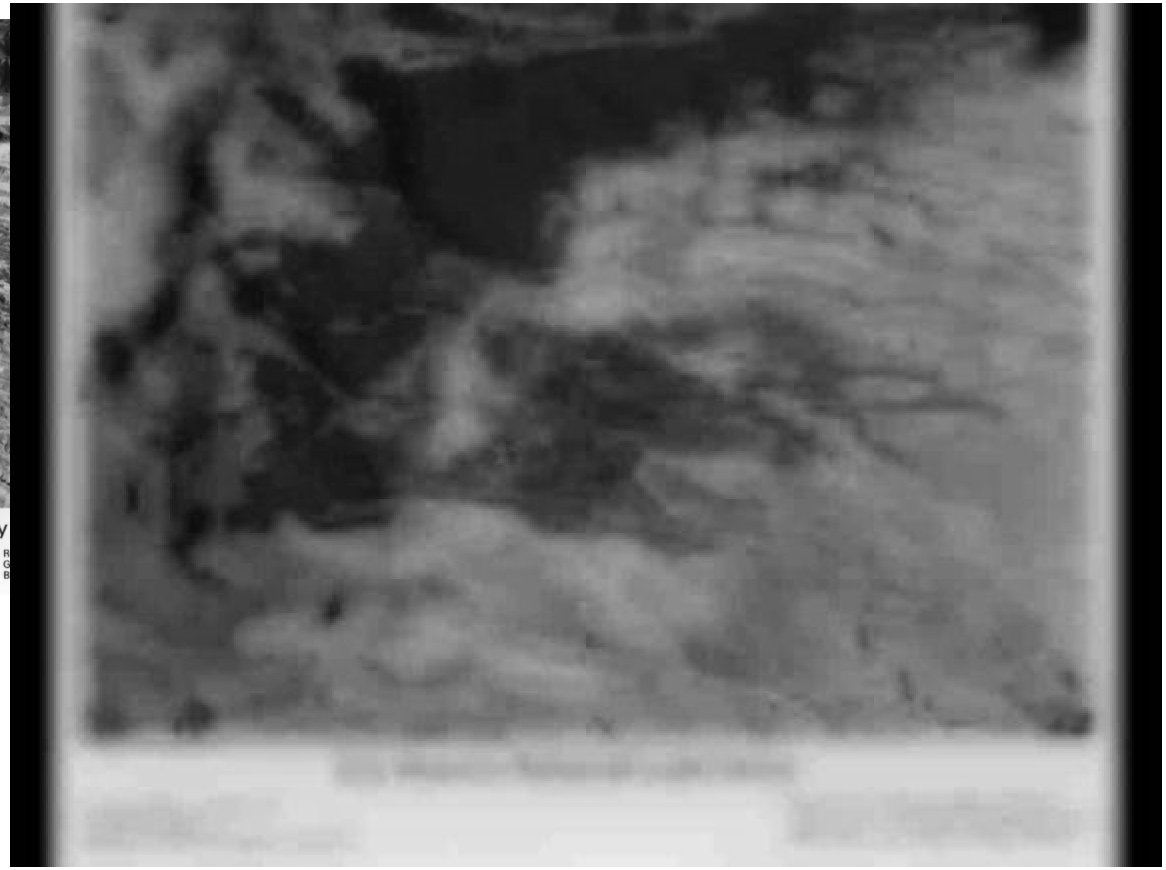
The Power of Imagery



Spreading Depression Registered to Anatomy



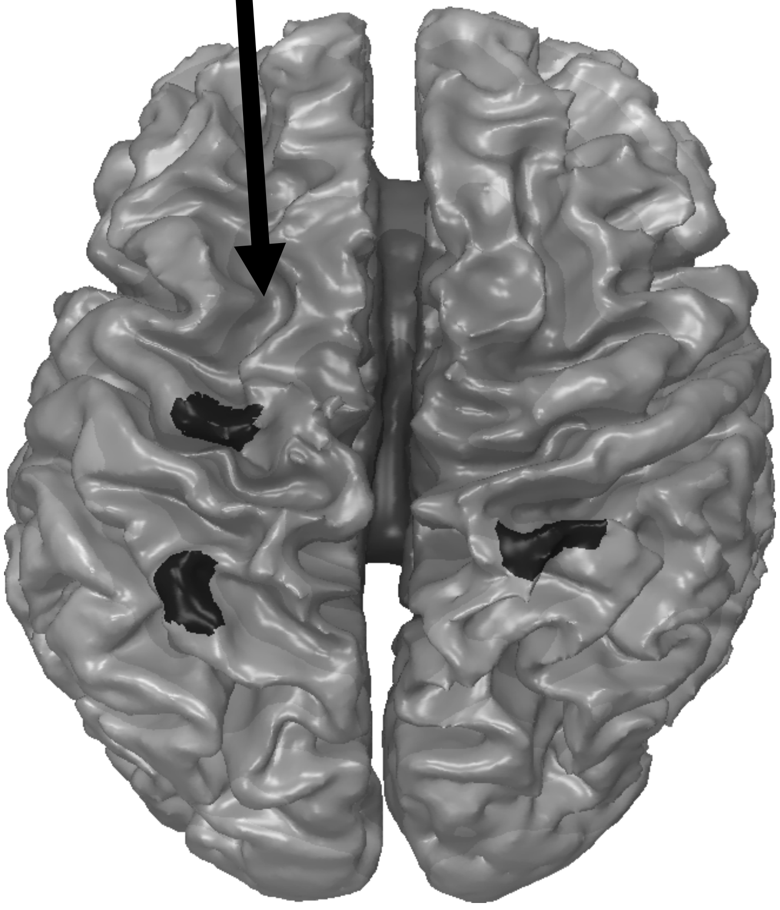
Spatial Blurring



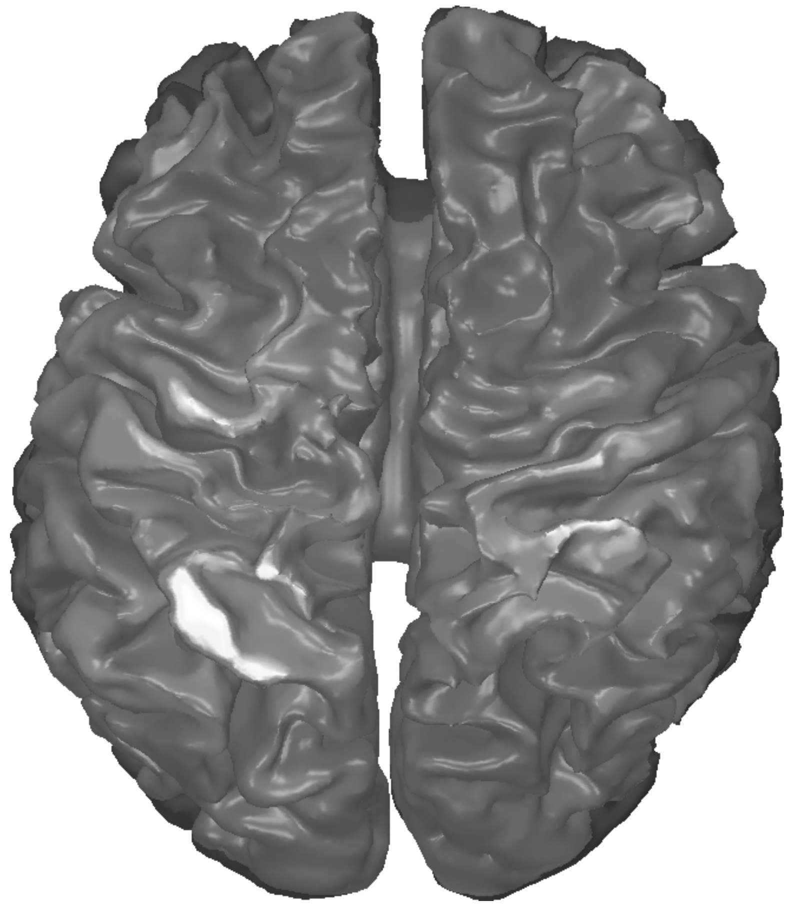
- Separation from source to measurement blurs image
- EEG/MEG are too far away: Total Spatial Loss
- “Images” are really low-order “models”

Modeling and Image Reconstruction

Occam's Razor



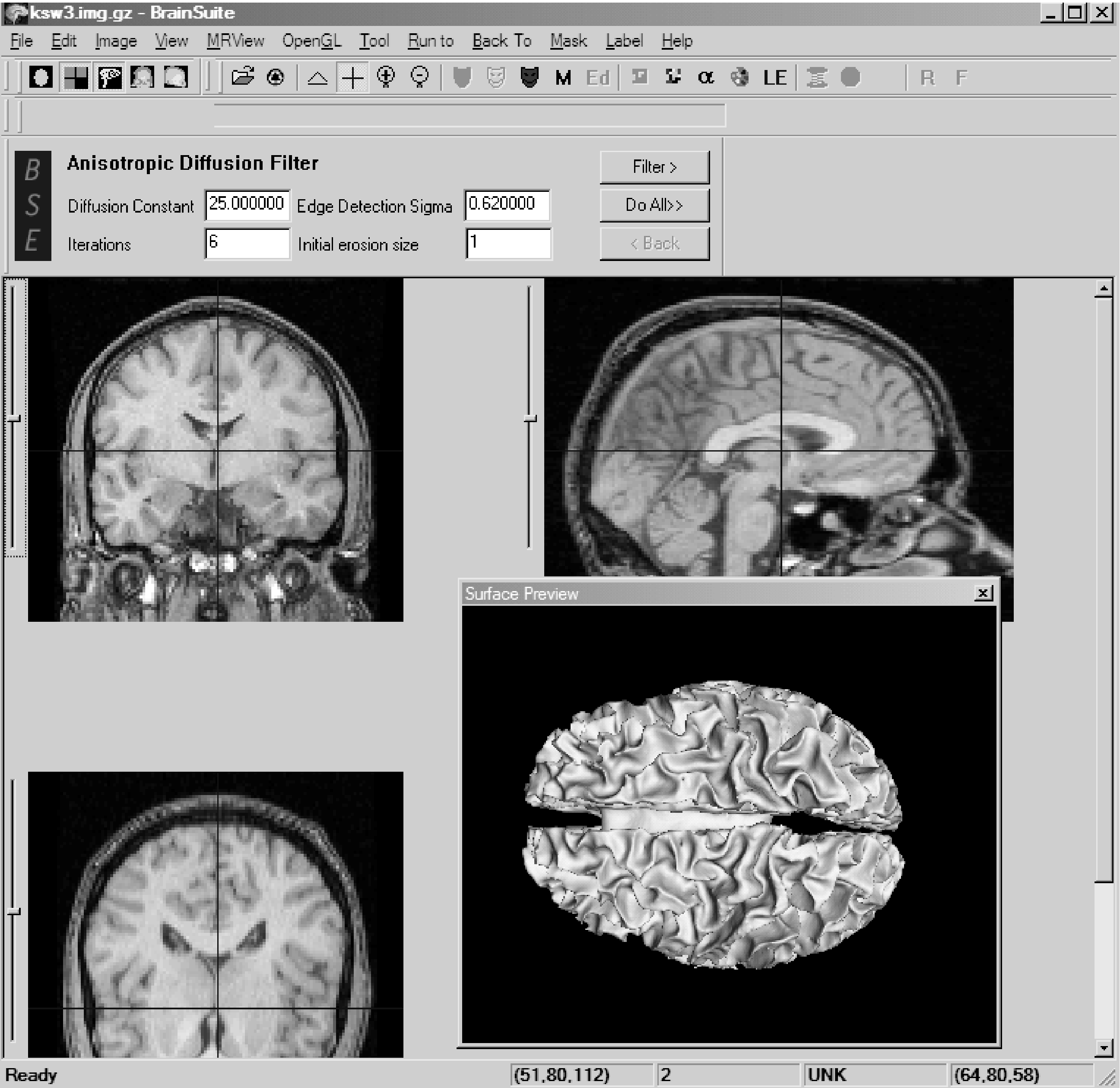
Model 1



Model 2

BrainStorm

Dr. John C. Mosher, Los Alamos National Laboratory



BrainSuite

- Surface extraction, with bias field and topological corrections.
- ~Automated scalp, skull, cortex tesselations
  - Started at USC by David Shattuck, now at UCLA-LONI program (Art Toga).

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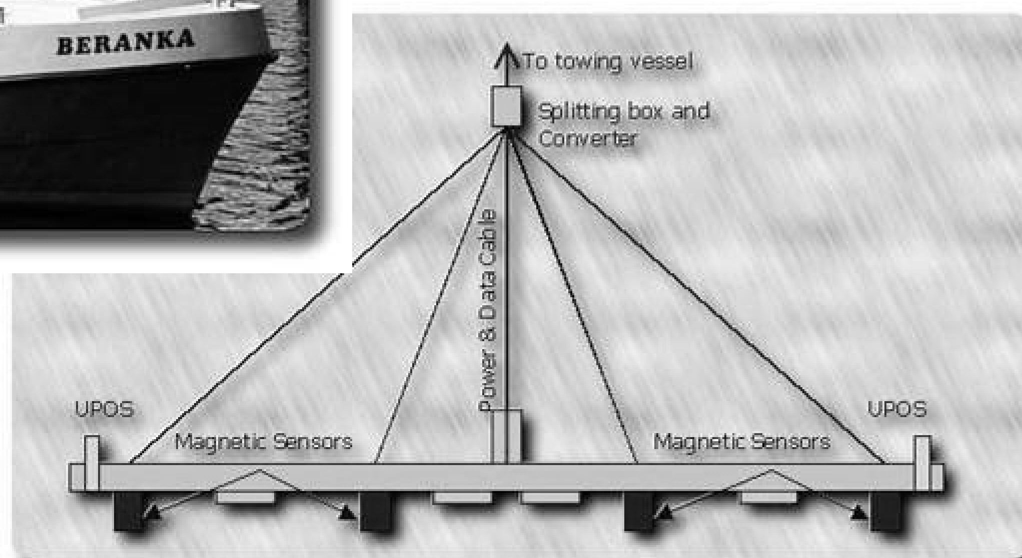
Ocean Magnetic Anomaly Measurements

Geopro.com



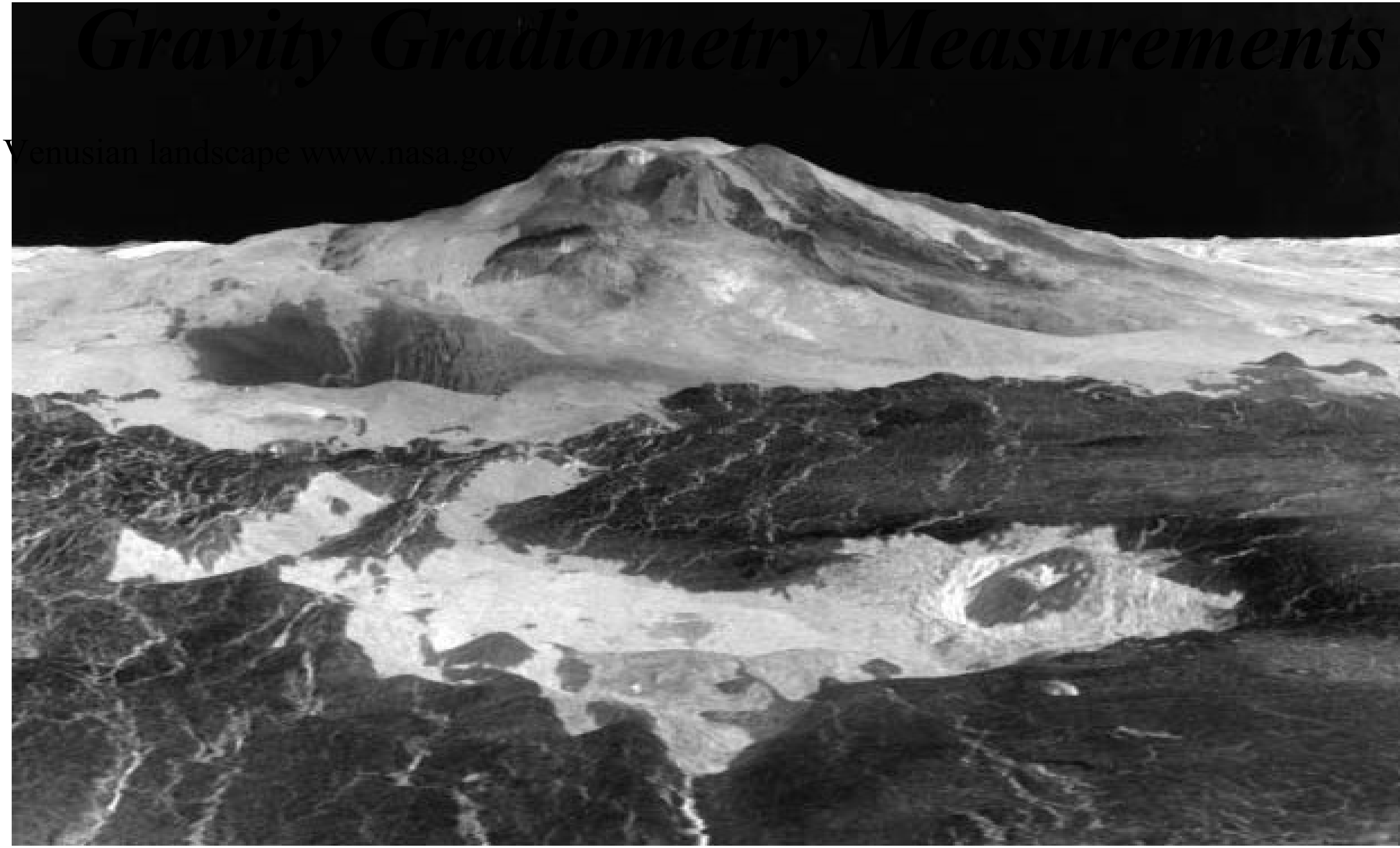
Aeromagnetic Measurements

- 50,000 - 60,000 nanoTeslas nominal Earth Field.
- Brain is sub picoTesla.

www.usgs.gov

- Measurement looks for differences from the static model.
- Airborne or satellite.

Gravity Gradiometry Measurements

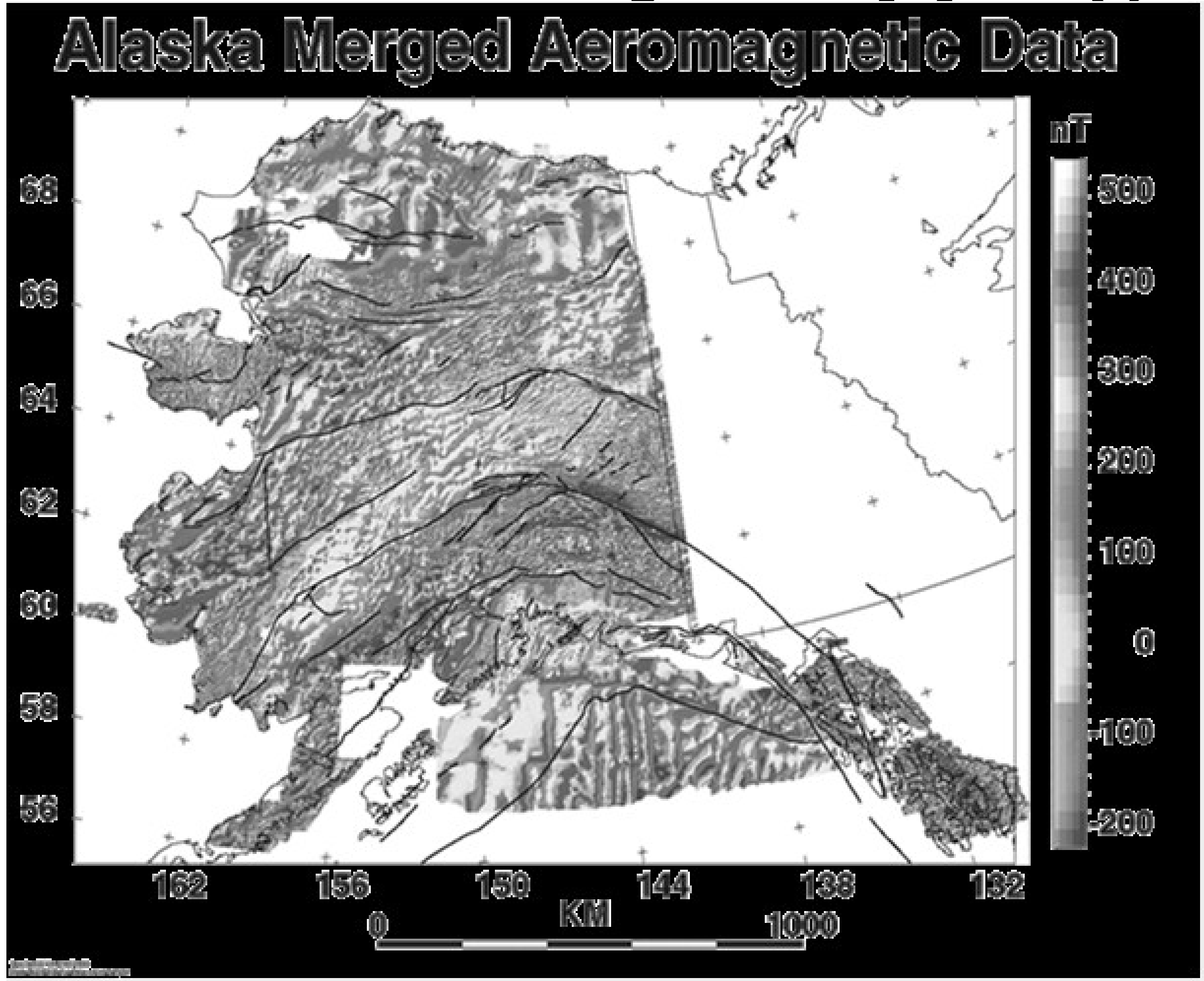


Venusian landscape www.nasa.gov

- Space Shuttle or Satellites measure micro-accelerations.
- **Models** help interpret changes in land masses below.

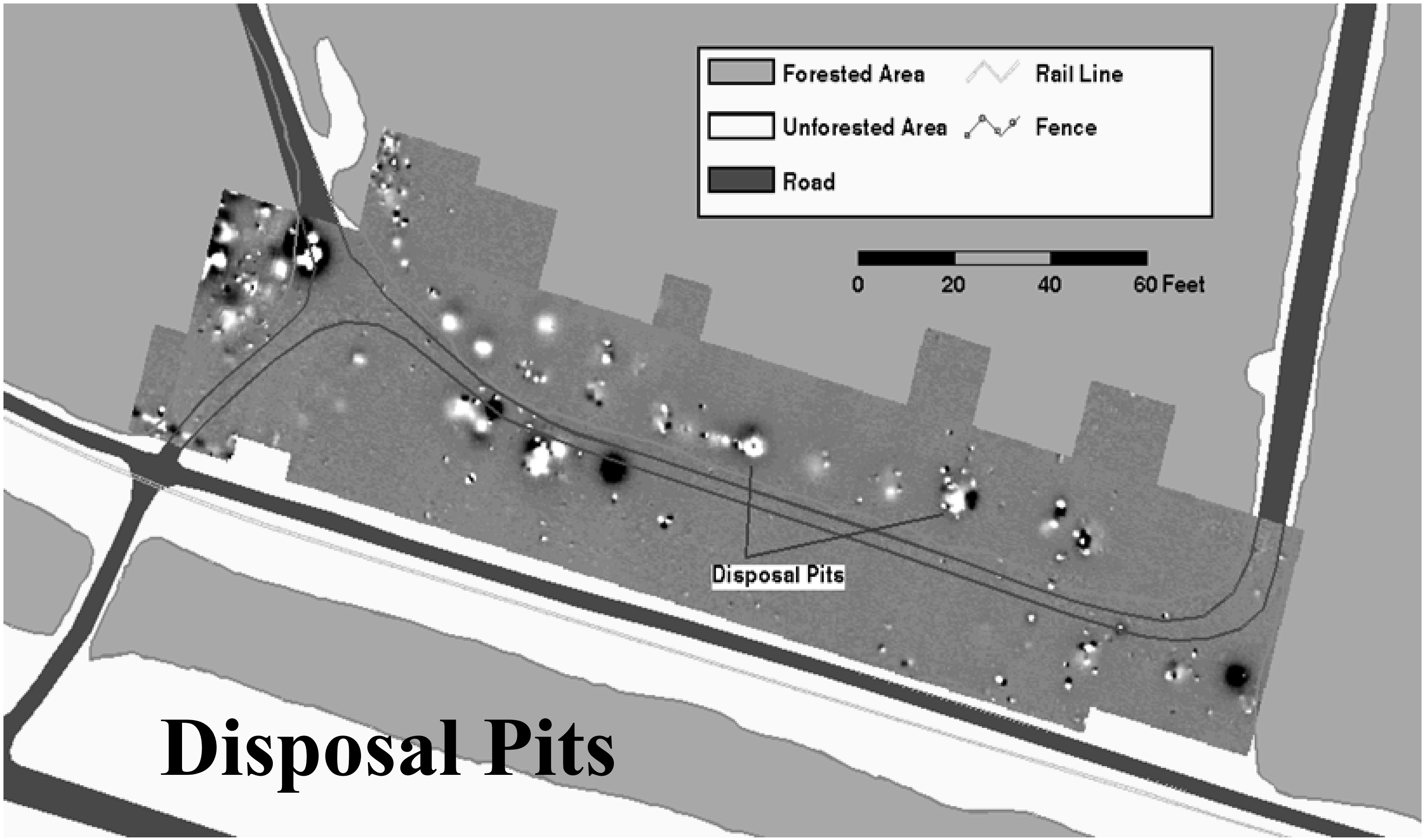
Anomaly Mapping

www.usgs.gov



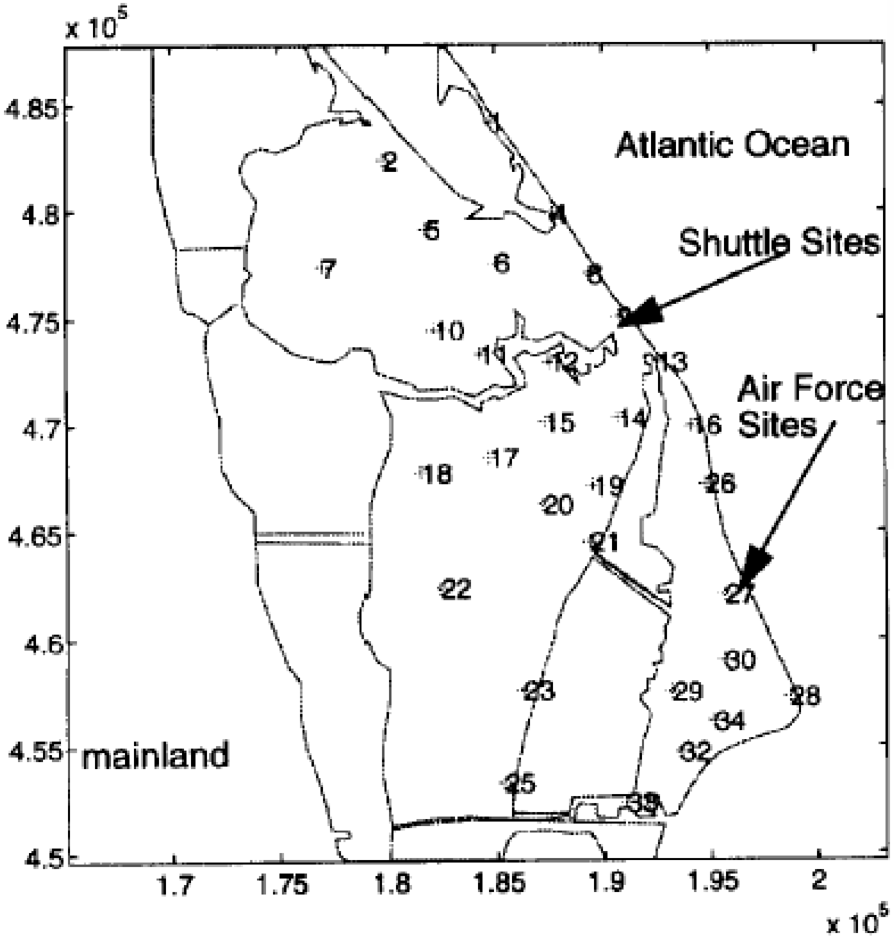
- When combined with geographic data and fault lines, adds to the understanding in geophysical exploration.
- NanoTesla anomalies shown.

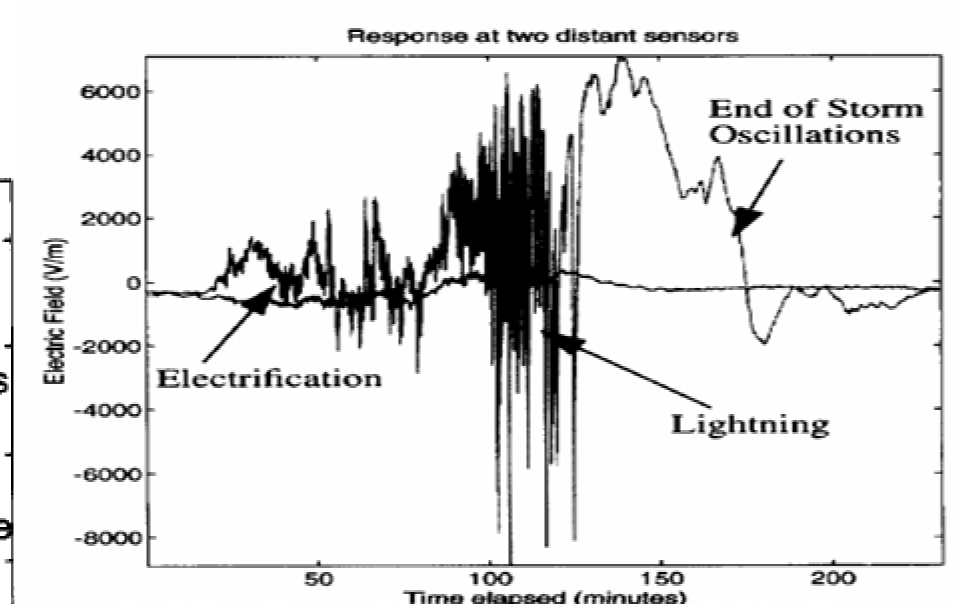
Magnetic Site Surveys

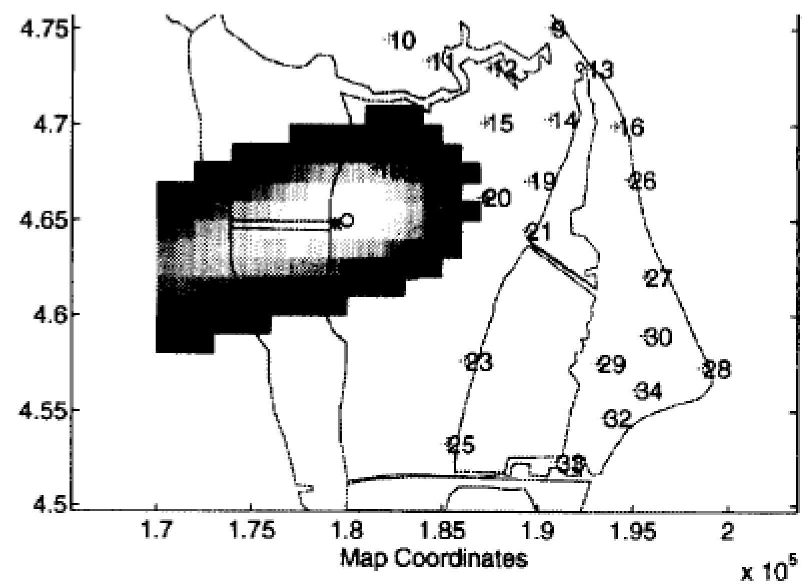


Argonne National Laboratory

Thunderstorm Localization

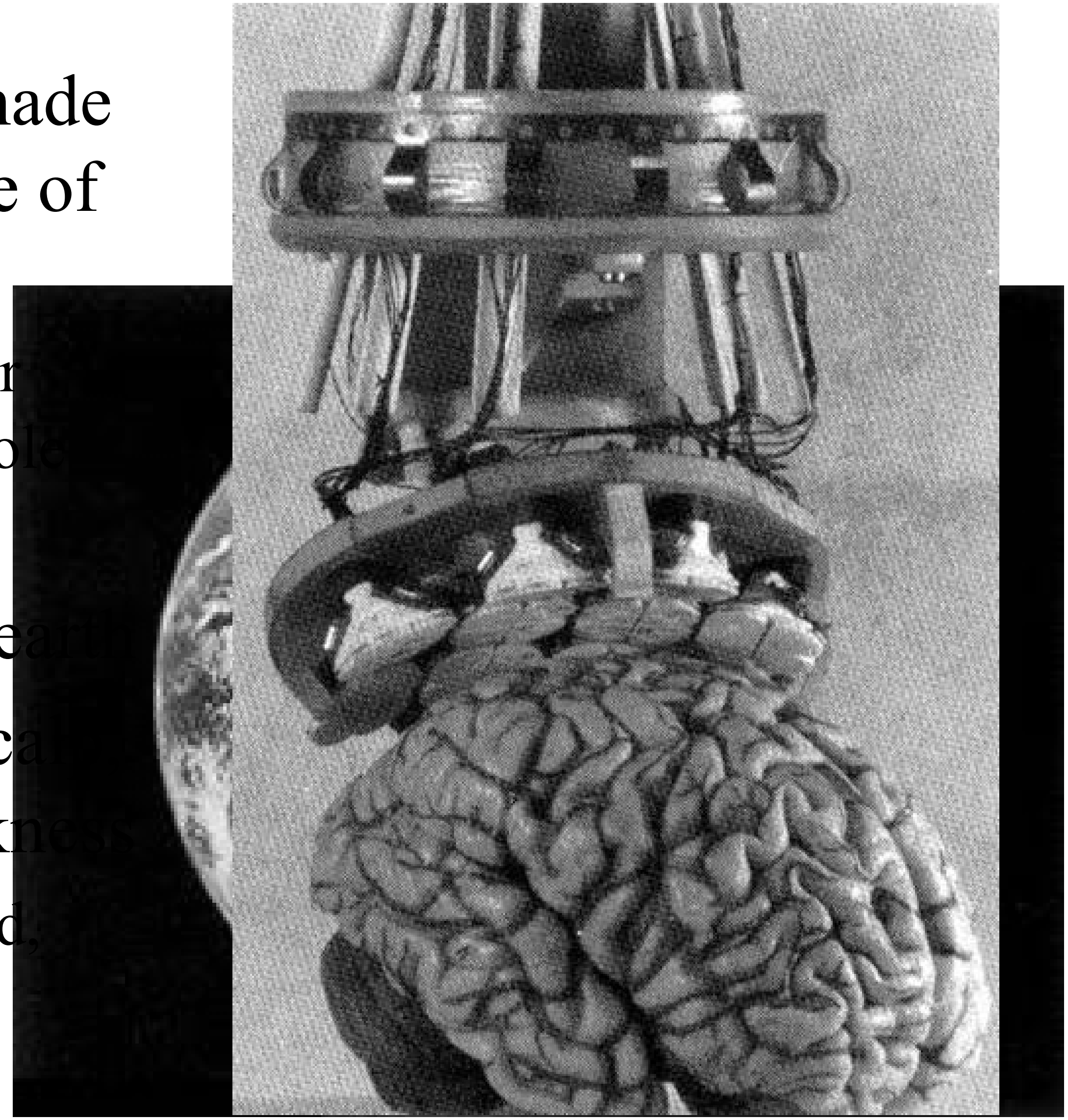




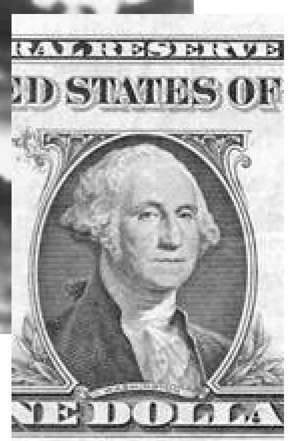


Measurements from a Distance

- In each case, the measurements are made at a distance, outside of a “forbidden zone.”
  - Earth is a sixth-order gravitational multipol
- “Forbidden zones:” atmosphere, ocean, e
- MEG/EEG: skull, sca air gap, Dewar thickn
  - One meter from head, magnetic dipole



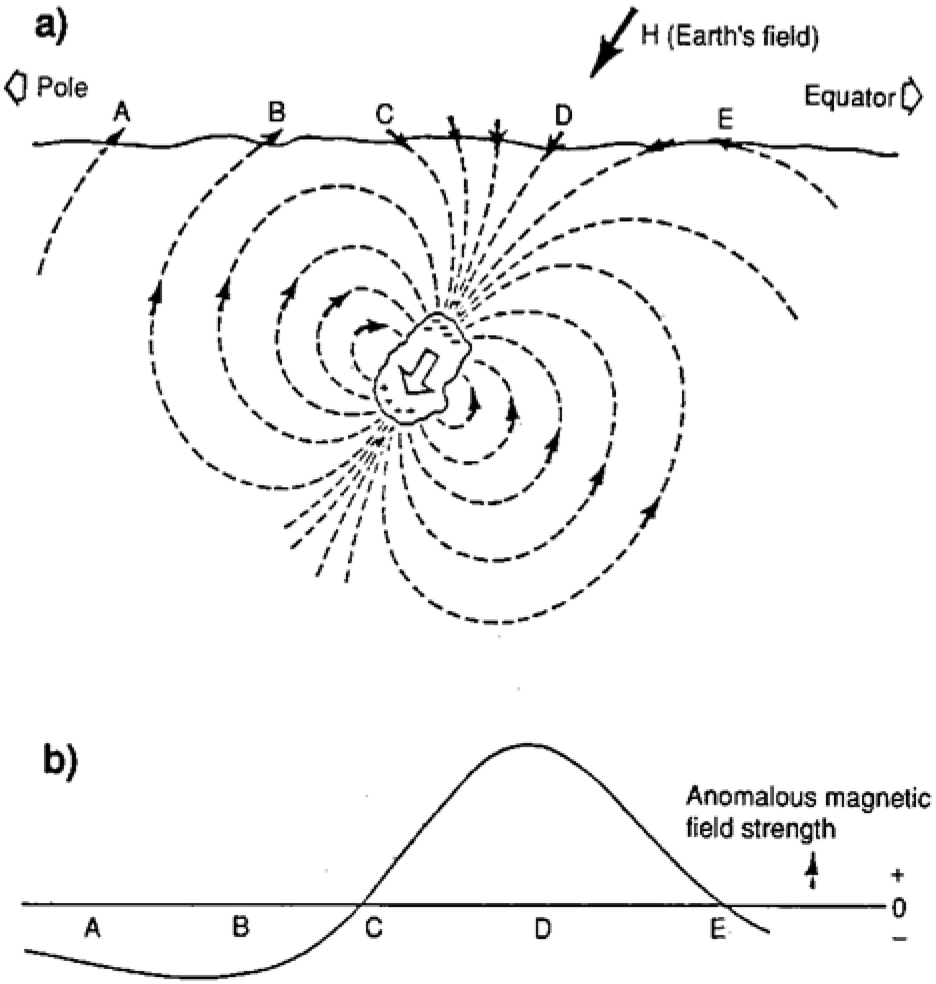
Magnetic Imaging



Center for Superconductivity, Univ. Maryland

- "SQUID Microscopes"
- Washington on the dollar bill.
- Density of ferromagnetic ink.
- Separation distance on the order of 100s of microns.
- MEG separation is centimeters.

Basic Source Model



- Buried or distant objects with anomalous gravitational or magnetic properties.
- Ambiguity between size, depth, and intensity.
- Models combined with other modalities.

www.usgs.gov

Newtonian Potential

$$k\frac{\text{Mass}}{\text{Distance}} \qquad f(r) = k \int_{\text{volume}} \frac{\text{density}(r')}{|r - r'|} dr'$$

- Measured field is proportional to the mass divided by the distance.
- For "near" distances, replace mass with mass density and integrate over the volume of the mass.

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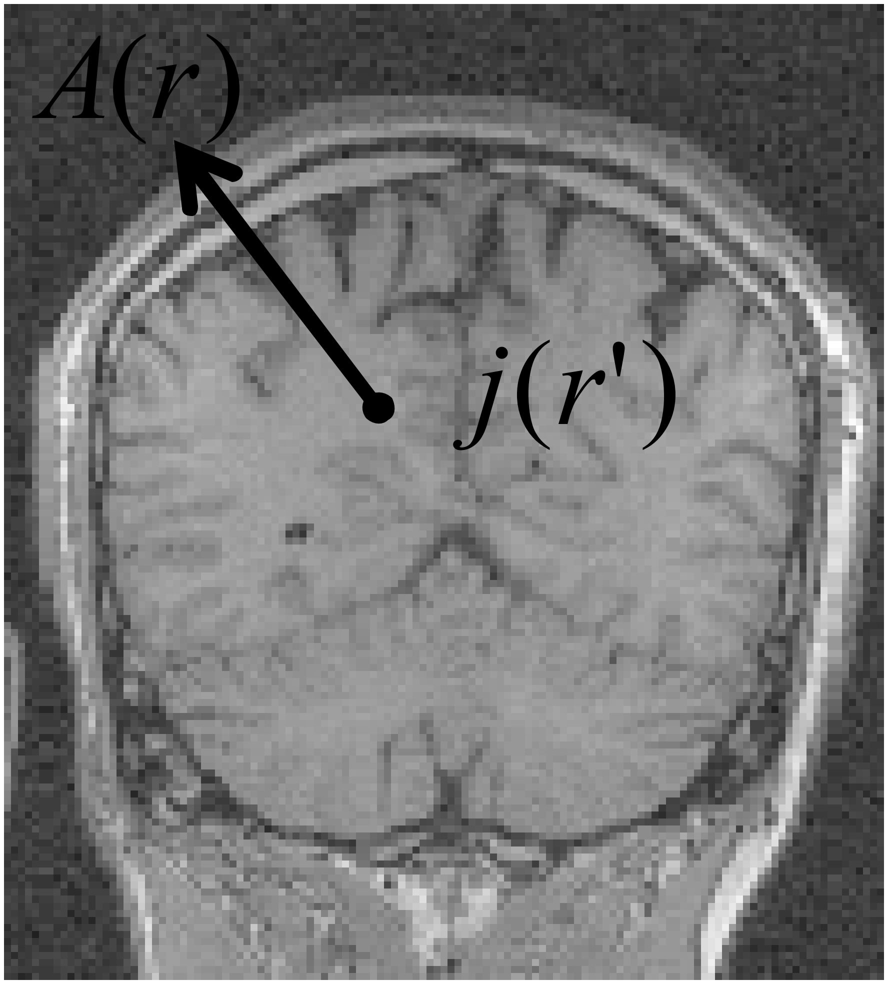
Magnetic Vector Potential

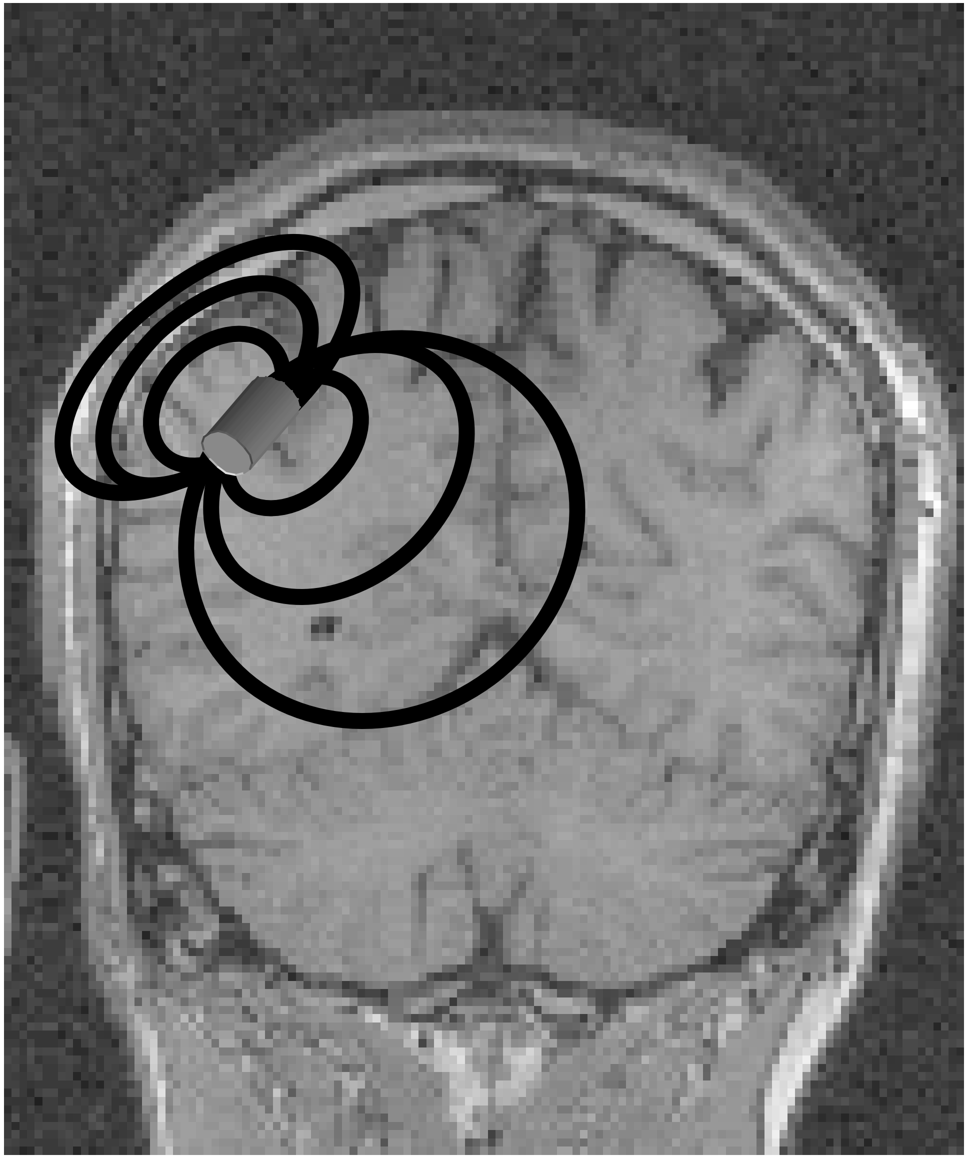


BrainStorm

$$A(r) \approx \int_{\text{head}} \frac{j(r')}{|r - r'|} dr'$$

- Integrate the ***total*** current density flowing in the head, divided by its distance to the observation.
- Minimum distance is "forbidden zone."

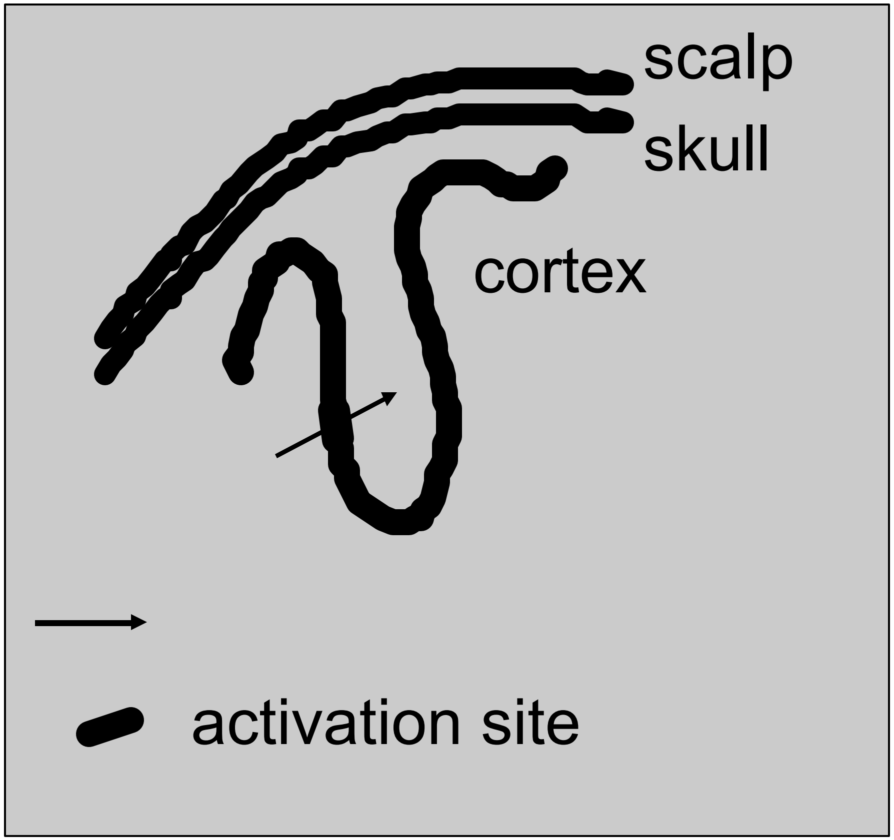
Primary vs. Secondary Currents



BrainStorm

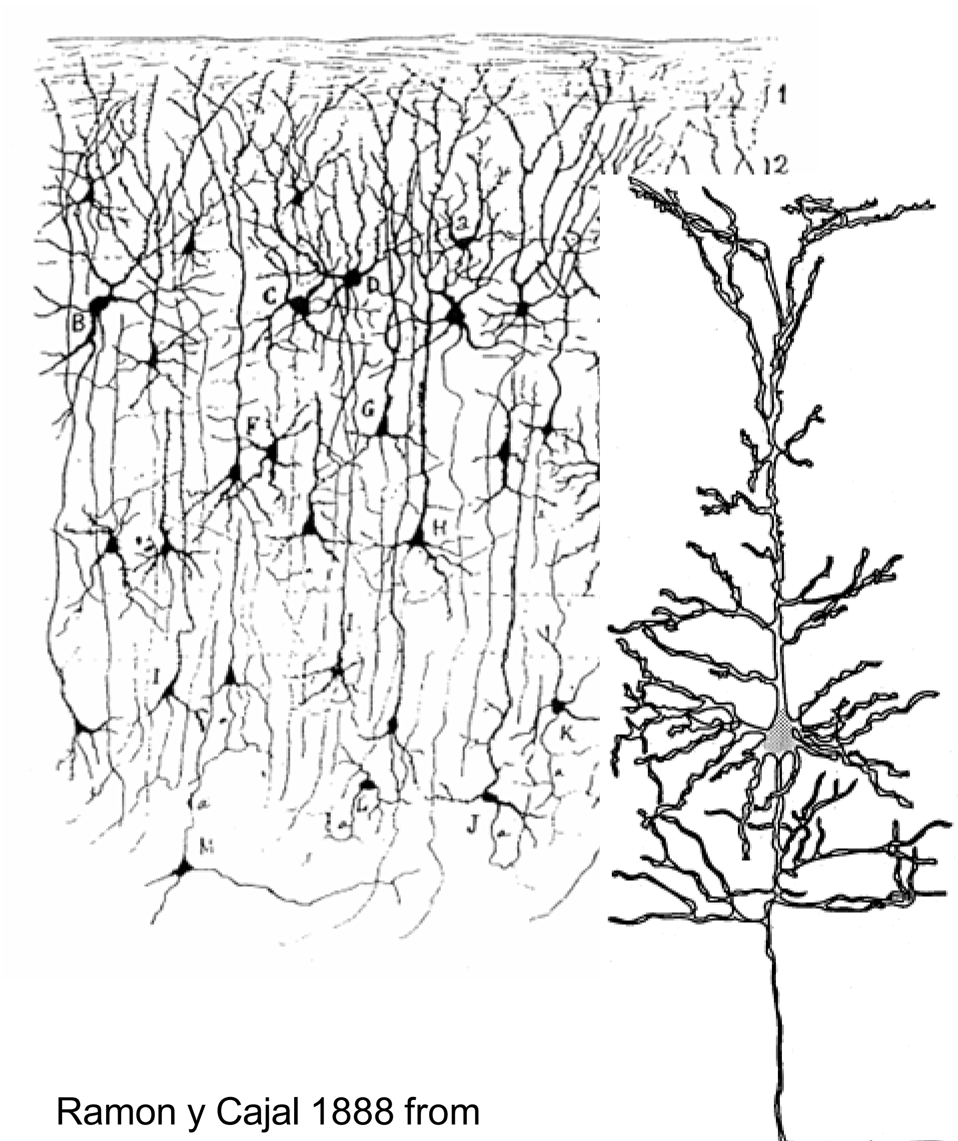
- Picture ***primary current*** as a small battery inside the brain.
- Secondary or volume currents are the gradient currents to “complete the circuit.”
- Primary = NOT secondary
- All current fields must contain a primary component, not necessarily a gradient component (e.g., loop).
- Boundaries shape the volume currents.

Cortical Constraints



- The putative source of E/MEG recordings is the gray matter.
- Columnar organization of cortex and functional specialization on cortical surface lead to **current dipole model** to represent focal regions of activation.

Primary Neural Sources



Ramon y Cajal 1888 from
Hamalainen et al. 1993
Reviews of Modern Physics

- Primary currents are produced by current flow in apical dendrites in cortical pyramidal neurons.
- Millions of EPSPs summed over ~ten milliseconds.
- "Macrocellular" vs. "microcellular."

Cortical Surface Current Density

- Individual EPSP generates 20 fA-m primary current
- 10 nA-m observable suggests millions of EPSPs
- Surface current density about 100 nA/mm^2 (order of magnitude)
- e.g. 5mm x 5mm x 4mm thick cortical patch = 10,000 nA-mm = 10 nA-m

Calculations from
Hamalainen et al. 1993
Reviews of Modern Physics

Measured Electromagnetic Fields

Primary vector potential

$$A^p(r) \approx \int_{\text{head}} \frac{1}{|r-r'|}\, j^p(r')dr'$$

CURL: Homogeneous magnetic field

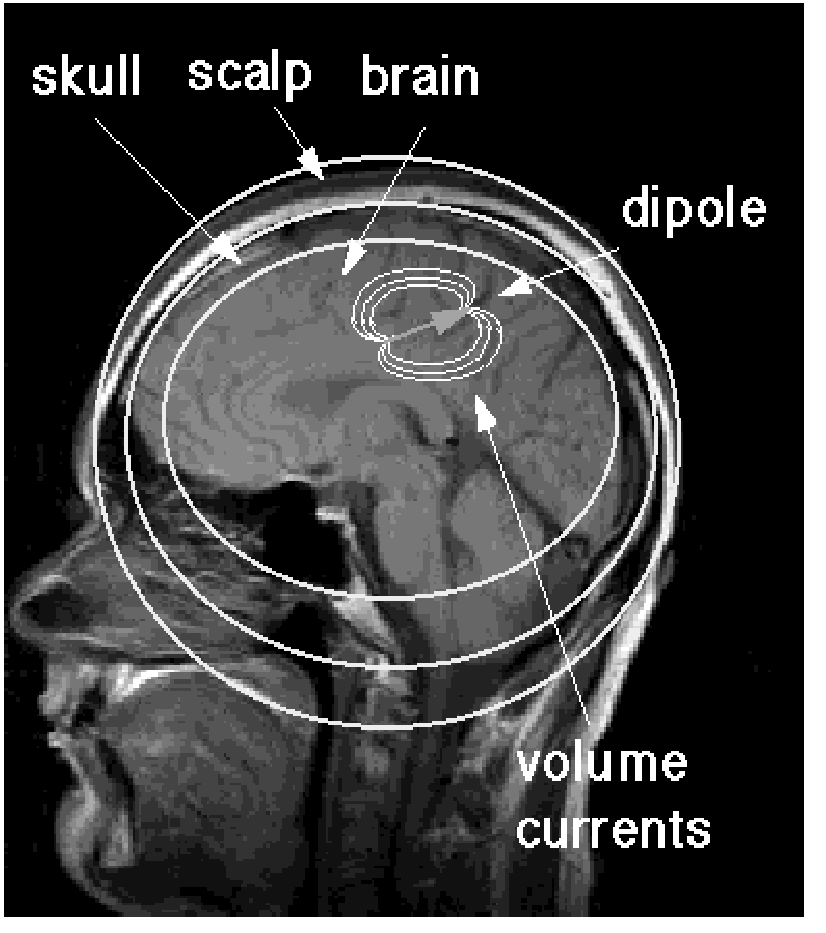
$$B^p_\infty(r) \approx \int_{\text{head}} \nabla\left(\frac{1}{|r-r'|}\right)\times j^p(r')dr'$$

DIVERGENCE: Homogeneous electric potential

$$v^p_\infty(r) \approx \int_{\text{head}} \nabla\left(\frac{1}{|r-r'|}\right) \cdot j^p(r')dr'$$

MEG and EEG Forward Models

- Use quasistatic EM model.
- Express models in terms of “primary” rather than “total” currents.
- Spherical head: closed form.



BrainStorm

MEG Spherical Solution

$$b_r(\boldsymbol{r}) = \frac{m_0}{4p} \frac{\boldsymbol{r} \times \boldsymbol{r}'}{\left|\boldsymbol{r} - \boldsymbol{r}'\right|^3 r} \cdot \boldsymbol{q}$$

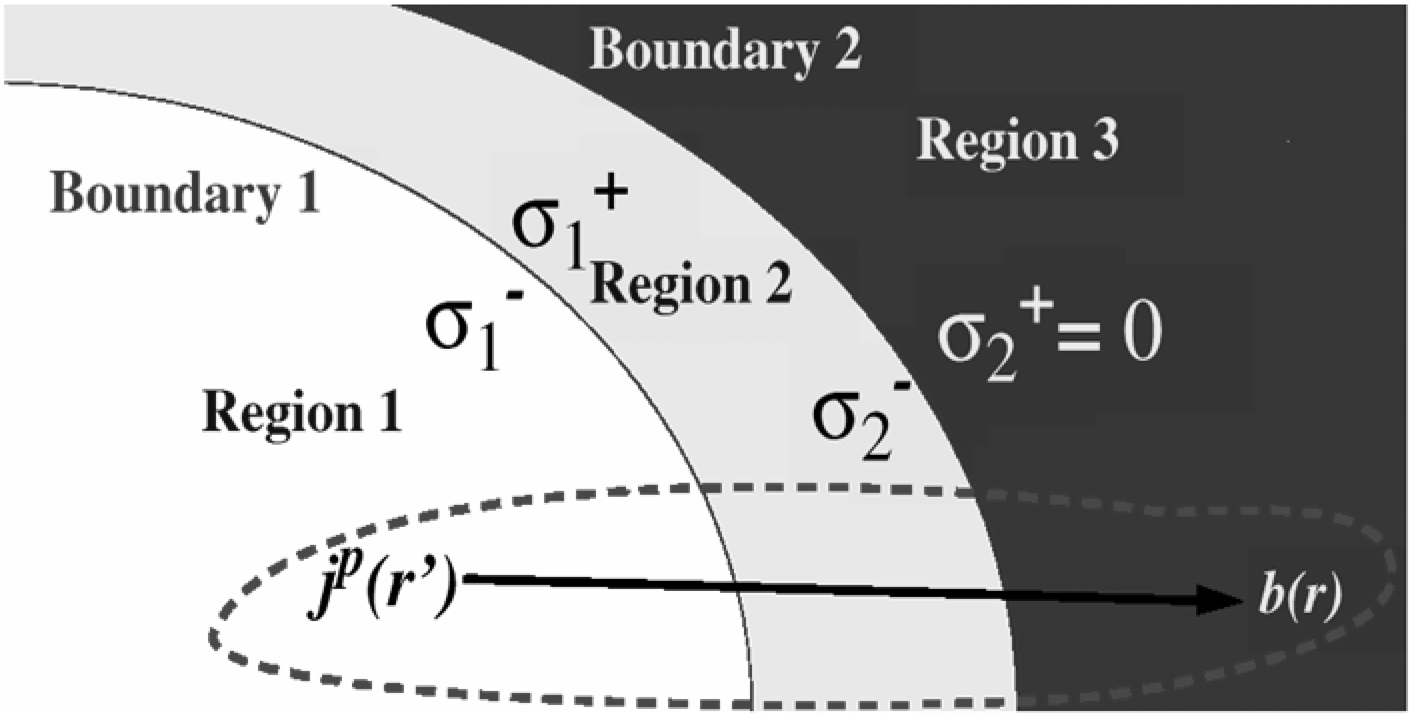
- Spherical head, radial MEG measurement at ***r*.**
- Dipolar source at ***r'***, moment ***q*.**
- Factored out are radii and conductivities.
- Non-radial direction also relatively simple in form.

Overlapping Spheres

BrainStorm Mingxiong Huang, UNM/VAMC

- Boundary element model requires upwards of 100s of megabytes.
- Overlapping spheres nearly as accurate, orders of magnitude faster.
- Both EEG and MEG.

General Boundary Problem



- Given primary current, what is the magnetic field?
- 3-D gradient currents map to 2-D surfaces as potentials.
- MEG general solution includes the general solution of EEG surface potentials.

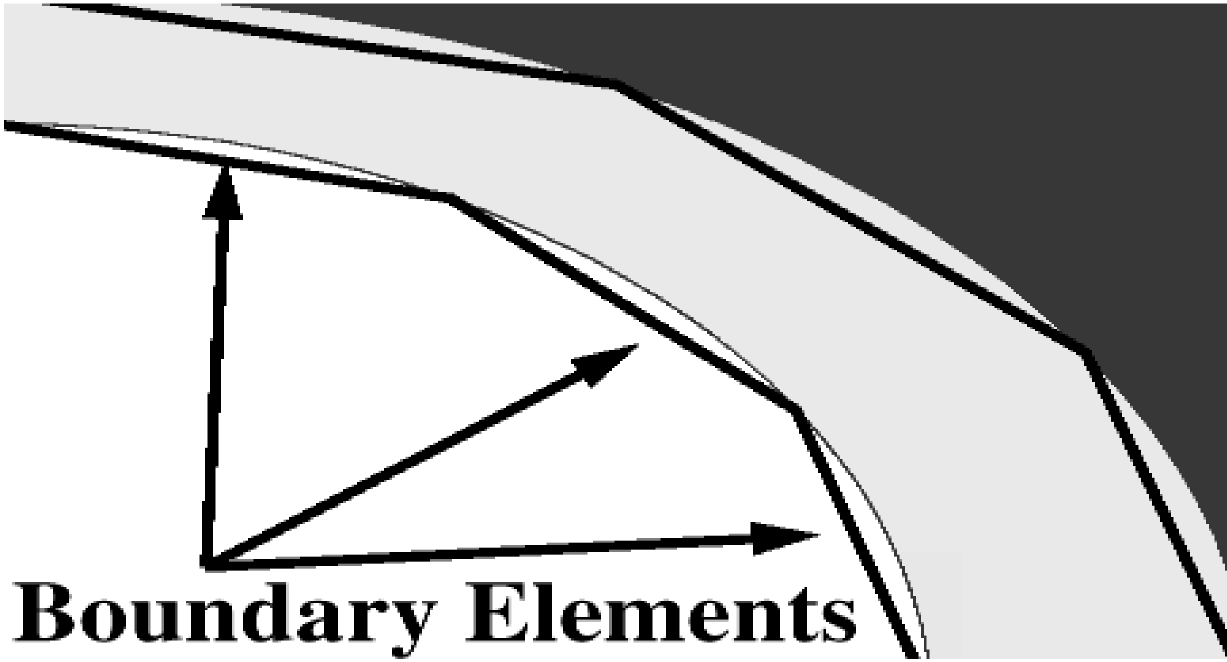
Fredholm Integral of 2nd Kind

- A specified primary current is the driving function $V_0(\boldsymbol{r})$
- Potential on all surfaces must be solved inside and outside an integral.

$$V_0(\boldsymbol{r}) \approx V(\boldsymbol{r}) + \sum_{ij} k_{ij} \int_{S_{ij}} V(\boldsymbol{r}') d\Omega(\boldsymbol{r}')$$

- In general, no analytic solution.

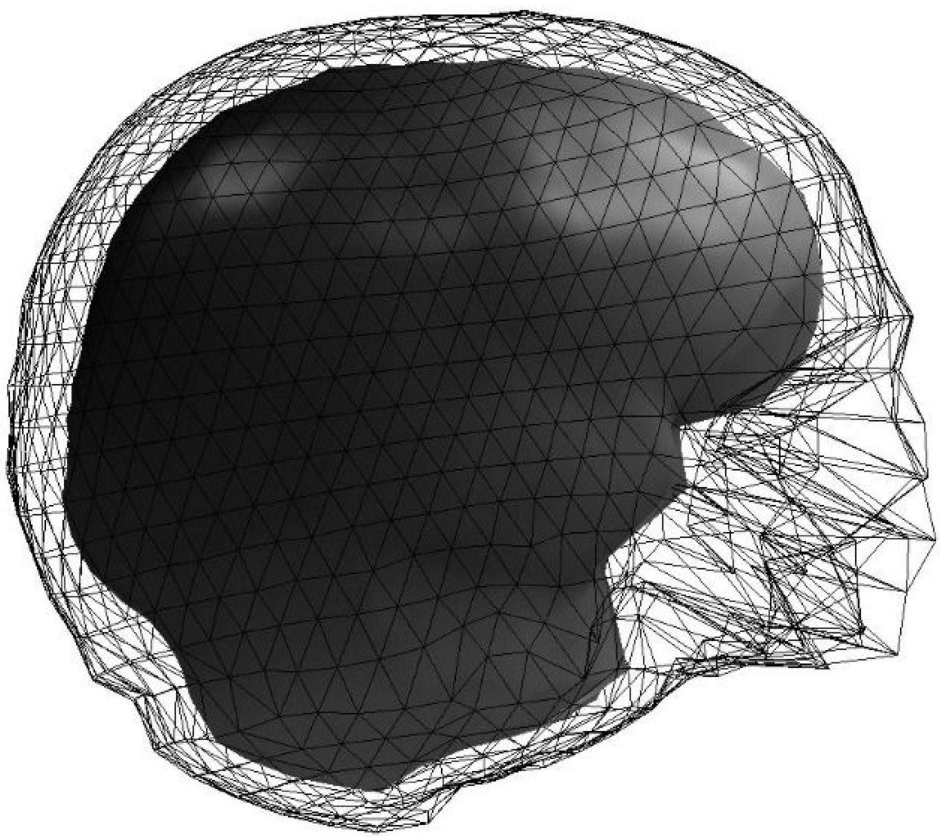
Numerical Boundary Element Solutions



- True surfaces are replaced with geometric elements, typically planar triangles.

- General solution replaced with thousands of simpler equations.
- Problems of thin skull and scalp layers.

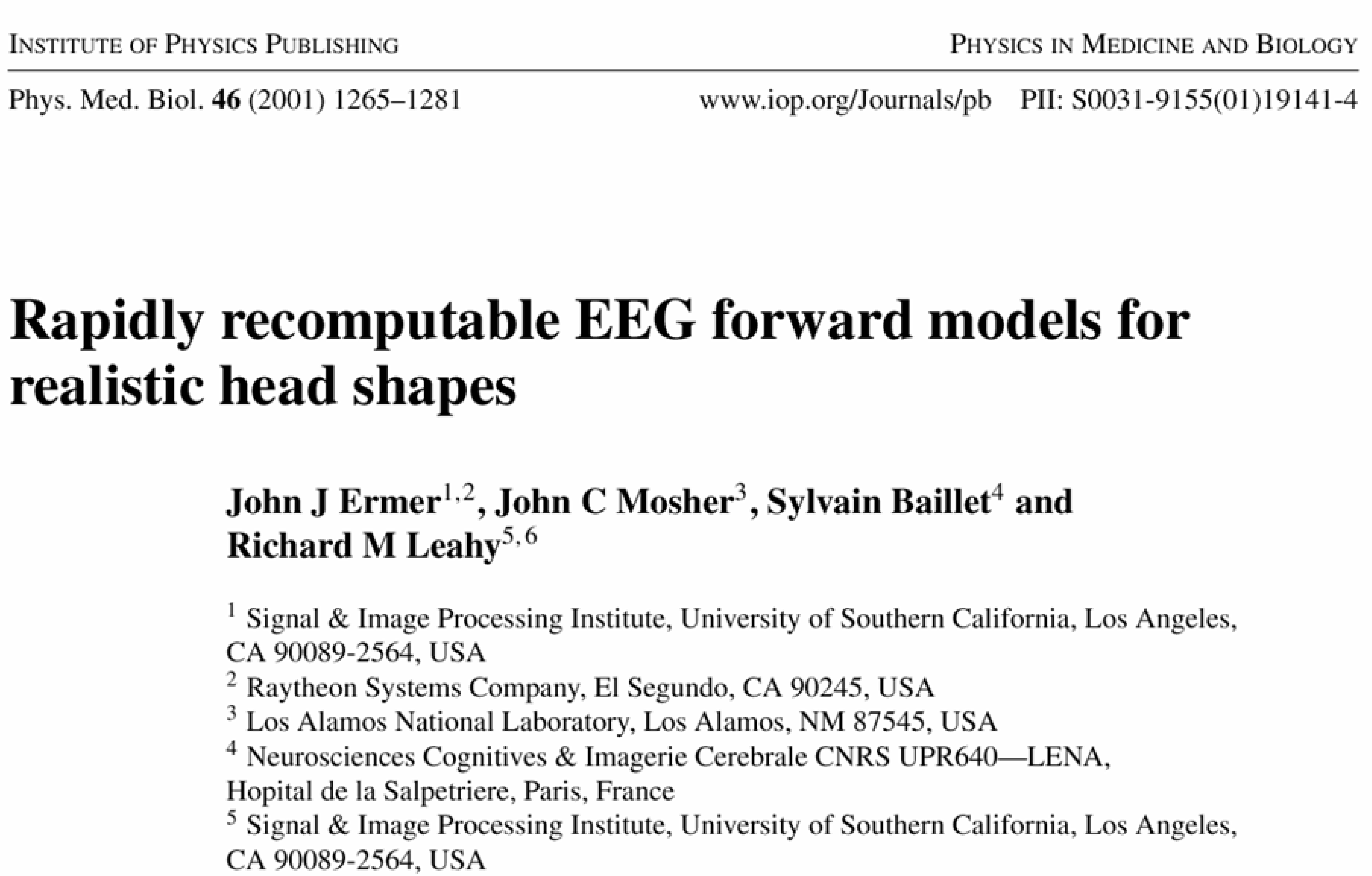
Surface Tessellations



BrainStorm

- Cortical surface, inner skull, outer skull, and scalp surfaces typically extracted.
- Example is 2,248 planar triangles over inner skull surface, similarly scalp surface.
- Approximately 80 Mbyte to generate.

BEM with Interpolation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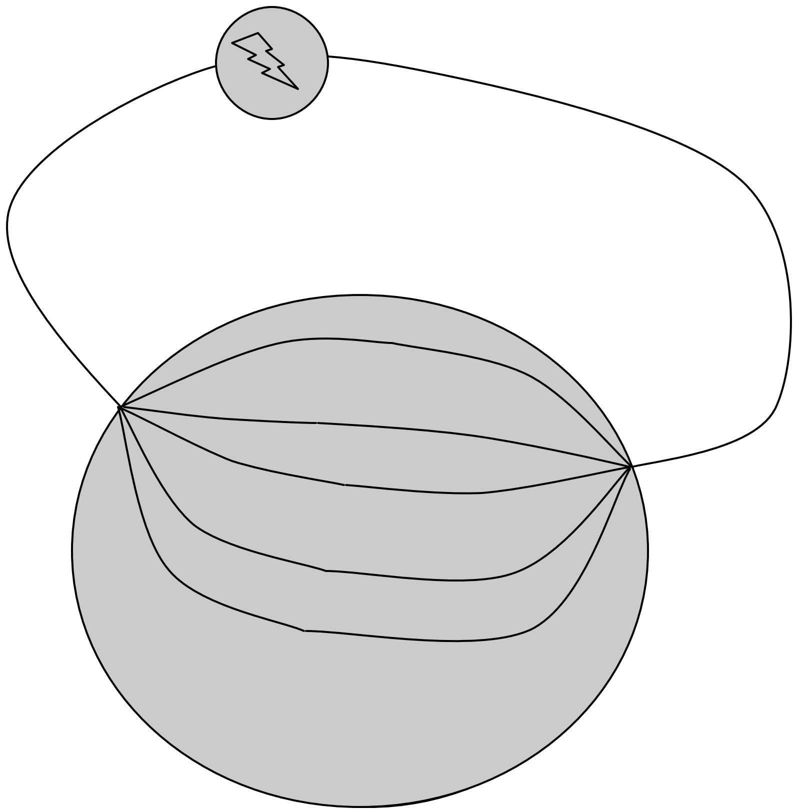
Phys. Med. Biol. **46** (2001) 1265–1281 www.iop.org/Journals/pb PII: S0031-9155(01)19141-4

Rapidly recomputable EEG forward models for realistic head shapes

John J Ermer[1,2], John C Mosher[3], Sylvain Baillet[4] and Richard M Leahy[5,6]

[1] Signal & Image Processing Institute, University of Southern California, Los Angeles, CA 90089-2564, USA
[2] Raytheon Systems Company, El Segundo, CA 90245, USA
[3] Los Alamos National Laboratory, Los Alamos, NM 87545, USA
[4] Neurosciences Cognitives & Imagerie Cerebrale CNRS UPR640—LENA, Hopital de la Salpetriere, Paris, France
[5] Signal & Image Processing Institute, University of Southern California, Los Angeles, CA 90089-2564, USA

Lead Field Analysis



$$\boldsymbol{L}_i(\boldsymbol{r})$$

- EEG: connect a pair of electrodes to the skull, apply voltage difference or current across the pair.
- The resulting currents fields are the “lead fields,” minimal energy currents.
- MEG: Use low-frequency alternating current in the gradiometer coils.

Reciprocity

- **<u>Lead Field</u>**: For a given external field stimulus (potential or magnetic field), what are the resulting currents throughout the conducting volume -> ***L(r)***.
- **<u>Forward Model</u>**: For a given channel (EEG or MEG), what is the measurement *m* observed for a given primary current dipole, ***q(r).***
- **<u>Answer</u>**: Measurement is simply an inner product between lead field and primary current dipole:

$$m_i = \boldsymbol{L}_i(\boldsymbol{r}) \cdot \boldsymbol{q}(\boldsymbol{r})$$

Linear Imaging

- Integration of lead field:

$$m_i = \int_{volume} \boldsymbol{L}_i(\boldsymbol{r}) \cdot \boldsymbol{q}(\boldsymbol{r}) d\boldsymbol{r}$$

- Discrete putative source regions:

$$m_i = \sum_{cortex} \boldsymbol{L}_i(\boldsymbol{r}_j) \cdot \boldsymbol{q}(\boldsymbol{r}_j)$$

- Matrix form:

$$\begin{bmatrix} m_1 \\ \vdots \\ m_M \end{bmatrix} = \begin{bmatrix} L_1(r_1) & \cdots & L_1(r_P) \\ \vdots & \ddots & \vdots \\ L_M(r_1) & \cdots & L_M(r_P) \end{bmatrix} \begin{bmatrix} q_1 \\ \vdots \\ q_P \end{bmatrix}$$

Linear Algebra Formulation

$$\boldsymbol{m} = \boldsymbol{G}\boldsymbol{j}$$

- **Rows** of $\boldsymbol{G}$ are samples of the lead fields, constrained to cortex. The dipoles are concatenated into $\boldsymbol{j}$.
- **Columns** of $\boldsymbol{G}$ are forward field for a single dipole, sampled at the sensor sites.

Data Model

- In addition to the measurement model, we must consider "noise:"
  - SQUID and other acquisition system noise
  - Environmental noise (far and near)
  - "Brain noise" (other unmodeled brain activity)

$$\boldsymbol{d} = \boldsymbol{m} + \boldsymbol{n} = \boldsymbol{G}\boldsymbol{j} + \boldsymbol{n}$$

Statistics of Noise

- We generally try to model the noise **<u>statistically</u>**. The most common assumptions (proven or not) are

$$E(\boldsymbol{n}) = \boldsymbol{0}, \quad E(\boldsymbol{n}\boldsymbol{n}') = \boldsymbol{C}_{\boldsymbol{n}}$$

- A more accurate noise model is often

$$\boldsymbol{d} = \boldsymbol{G}\boldsymbol{j} + (\boldsymbol{H}\boldsymbol{k} + \boldsymbol{n})$$

where $\boldsymbol{Hk}$ is other unmodeled sources.

Forward Problem: Gj + n

- Estimate noise statistics ***n*** accurately.
- Generate accurate channel model, ***G.***
  - Change of Boundaries
    - Sphere, spheres, boundary elements, finite elements
  - Numerical Accuracy of New Boundaries
    - MEG sphere analytic, EEG sphere "Berg" parameters, linear approx with Galerkin error
  - Speed of Calculation
    - Interpolation schemes of Biomag 2000
  - Noise Rejection distorts the lead fields and must be included in the lead field model.

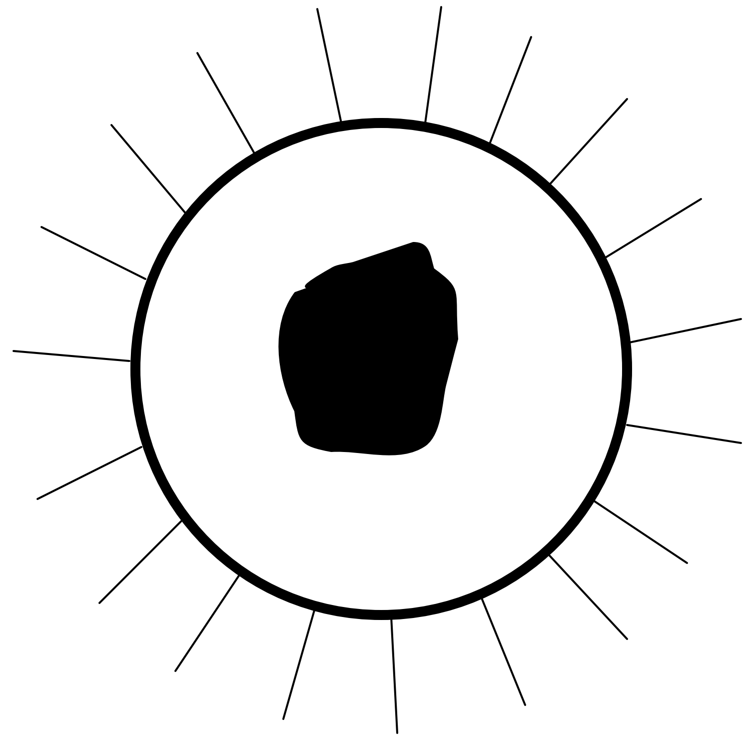
- <u>WITHOUT LOSS OF GENERALITY</u>:
  - WE ASSUME WE KNOW NOISE STATISTICS AND CHANNEL MODEL **PRECISELY**.

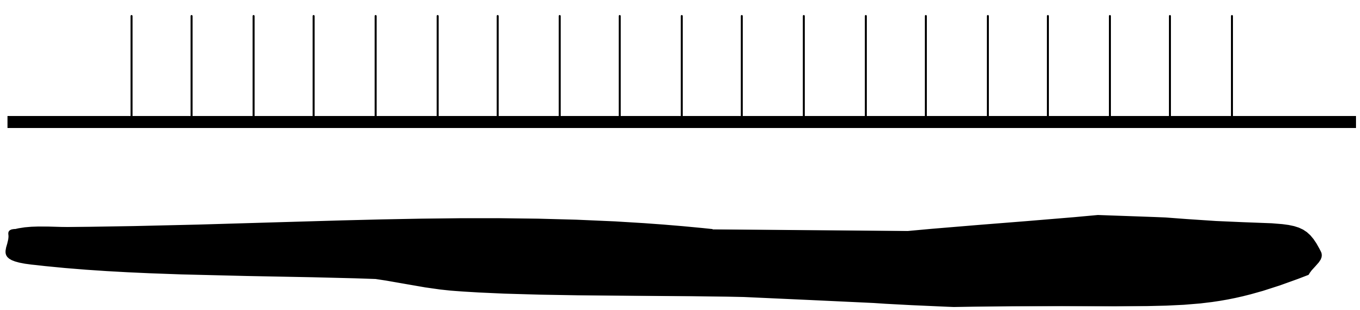
Outline

- “Imaging” vs. “Modeling” of data
- Similar Physical Sciences
- Forward Modeling
- Inverse Modeling
- Simulated and Experimental Results

Complete Knowledge

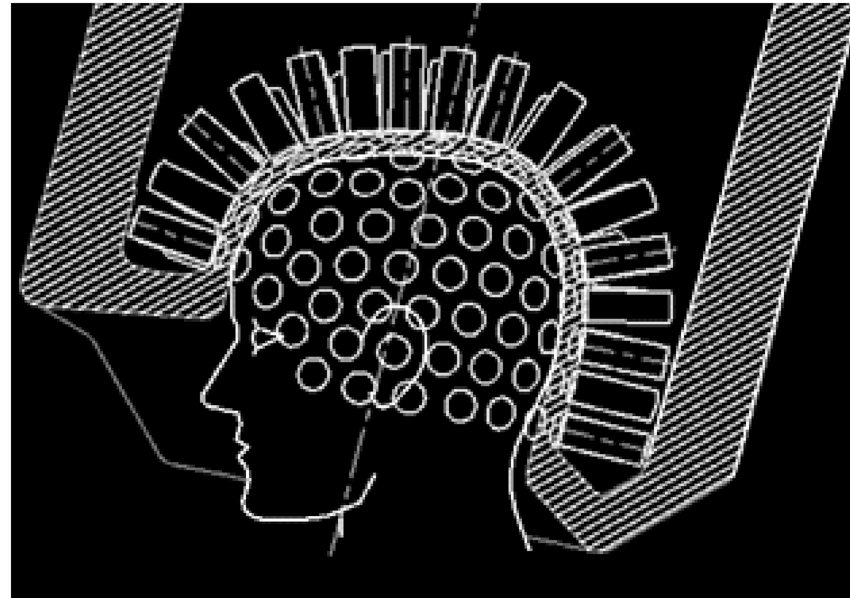
- If we know the source-free field normal to a closed bounding surface, then we know the source-free field everywhere.
  - RF fields require two such surfaces
- Basis of "downward continuation" schemes.

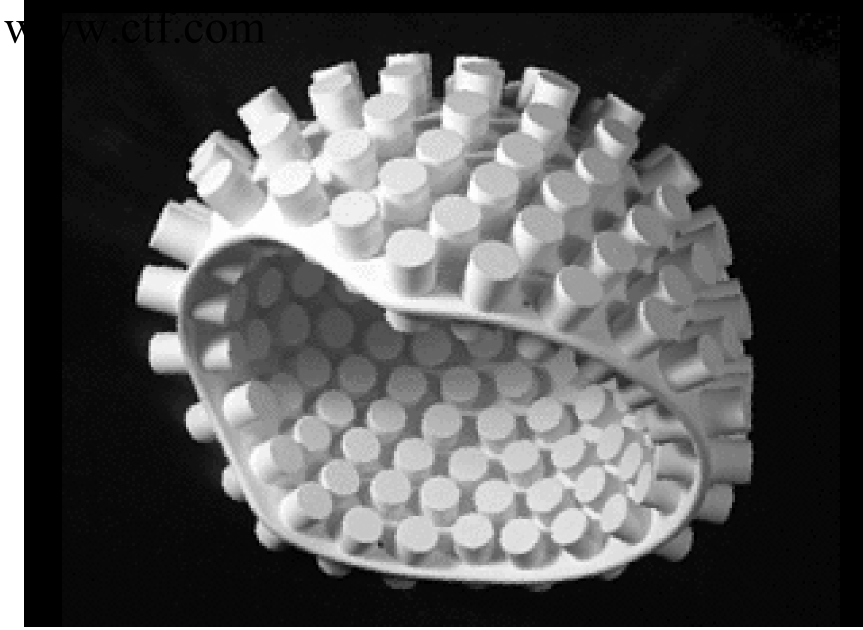




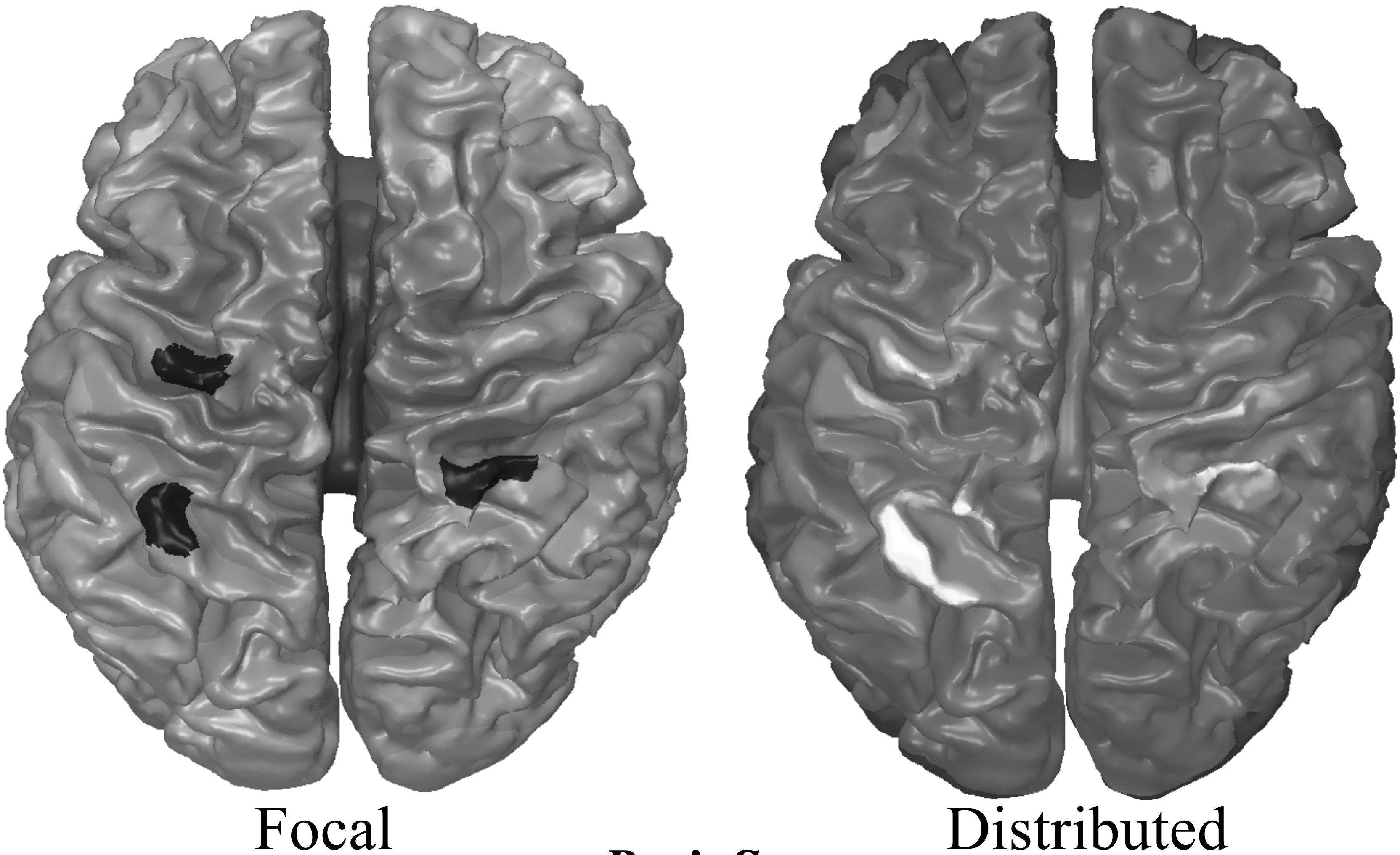
Incomplete Knowledge

- We know the field only on a helmet or cap, at discrete sites, with limited precision.
- Implicitly or explicitly, we must therefore:
  - Extrapolate the field in the missing solid angle.
  - Interpolate the field between the sensor points.
  - Regularize the imprecision.



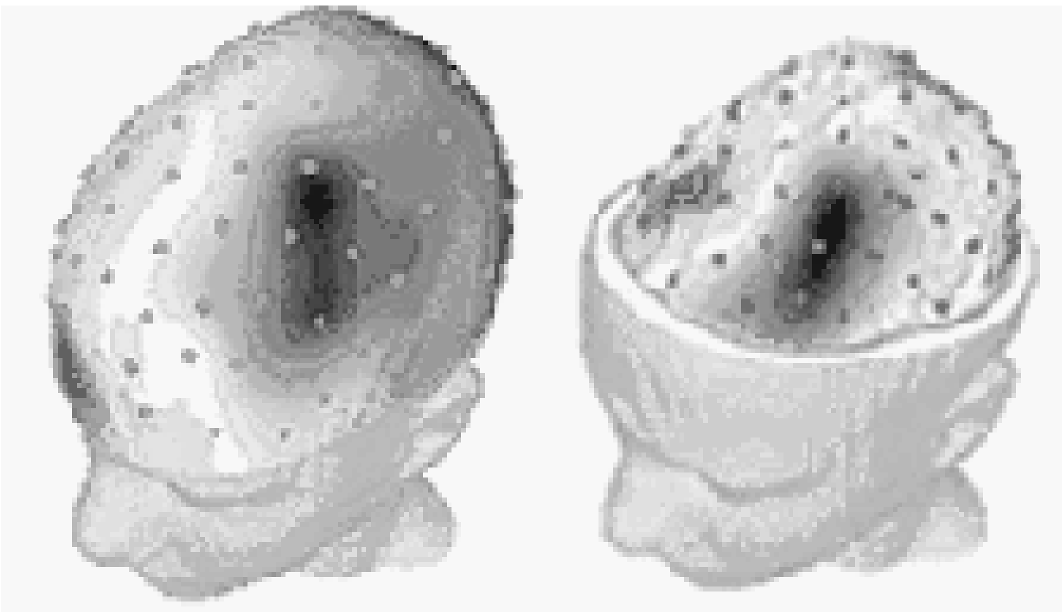


Dissimilar in Missing Regions



BrainStorm

Inward Continuation

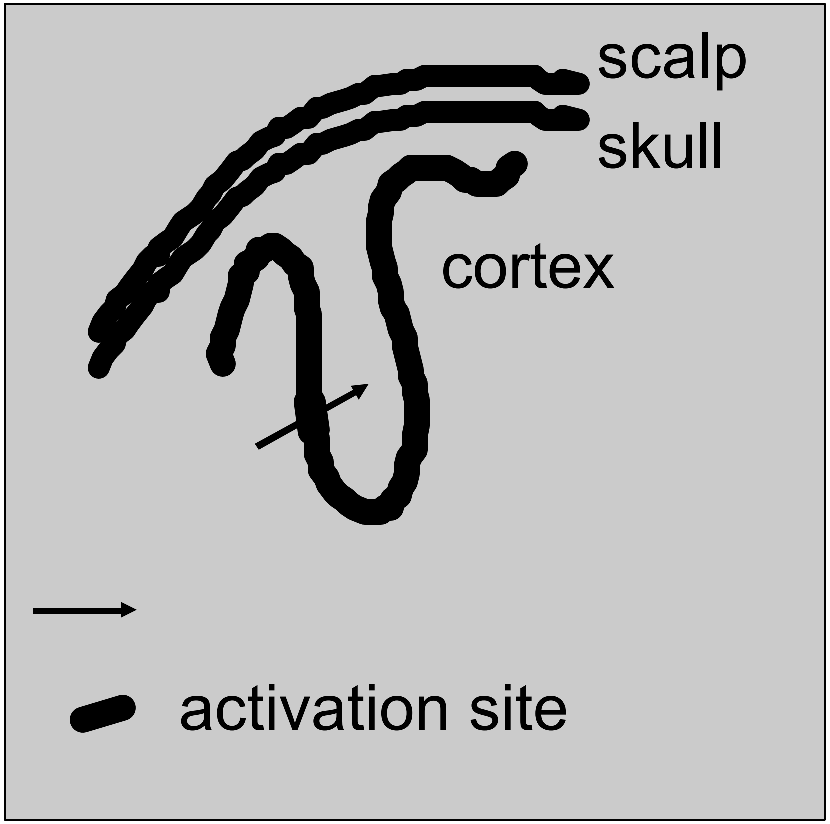


Gevins, EEG Systems Lab

- AKA deblurring, dura-imaging.
- In theory, surface potentials or fields are uniquely transformable to potentials on cortical surface.

• Boosts high-frequencies and noise, must generally be interpolated and regularized.

Inverse Methods: Imaging



- Place current dipole at each element in cortical surface tessellation.
- Linear inverse problem to estimate dipole amplitudes.
- Hugely underdetermined (10,000 unknowns vs. 100-300 measurements).

Minimum Norm Imaging Approach

- Let G represent the "transfer matrix" between dipole and measurement (the head model).
- Solve:

$$\min \; \|d - Gj\|_2^2 \; + \; l\,\|Wj\|_2^2$$

- Choice of weight function:
  - $\boldsymbol{W} = \boldsymbol{I}$: **minimum energy** solution
  - :$\boldsymbol{W} = \boldsymbol{W}_{norm} = diag\left[1/\|a_1\|, \ldots, 1/\|a_N\|\right]$: **column-weighted min-norm**
  - $\boldsymbol{W} = \boldsymbol{W}_{norm}\boldsymbol{B}$ where $\boldsymbol{B}$ also has the Laplacian operator: **LORETA**

Same: Linear Minimum Mean Square

- Assume estimate is a linear transform on the data.
- Assume 2^{nd} order statistics are known.
- Assume independence between noise and neural activity.
- Minimize the mean-square error.

LMMS, Also Known As:

$$\hat{\boldsymbol{j}} = \boldsymbol{C}_j \boldsymbol{G}^T \boldsymbol{C}_d^{-1} \boldsymbol{d}$$

$$= \boldsymbol{C}_j \boldsymbol{G}^T (\boldsymbol{G} \boldsymbol{C}_j \boldsymbol{G}^T + \boldsymbol{C}_v)^{-1} \boldsymbol{d}$$

- Linear Wiener-Hopf Solution
- “Weighted regularized minimum norm”
- MAP solution for Gaussian priors
  - Strong model dependence on source prior $\boldsymbol{C}_j$

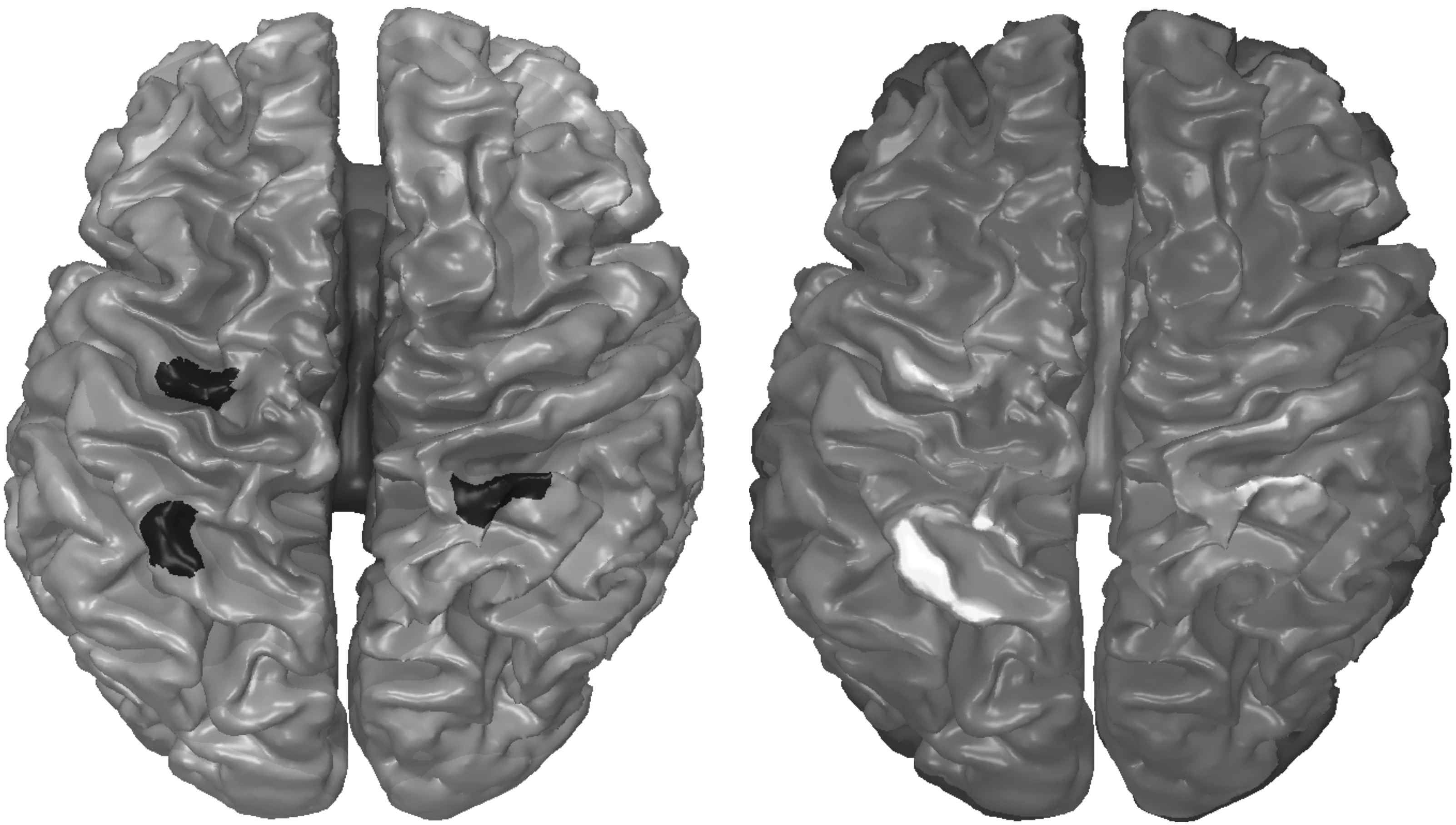
Limited Resolution

- Consider regularized minimum-norm solution:

$$\hat{j} = \sum_{i=1}^{M} \frac{s_i (u_i^T d)}{s_i^2 + l} v_i$$

- Where $\boldsymbol{G} = \sum_{i=1}^{M} s_i \boldsymbol{u}_i \boldsymbol{v}_i^T$ is the SVD.
- The basis images are a set of smooth functions and limit the resolution of this approach

Linear Imaging (Minimum Norm)



Simulated Estimated ***BrainStorm***

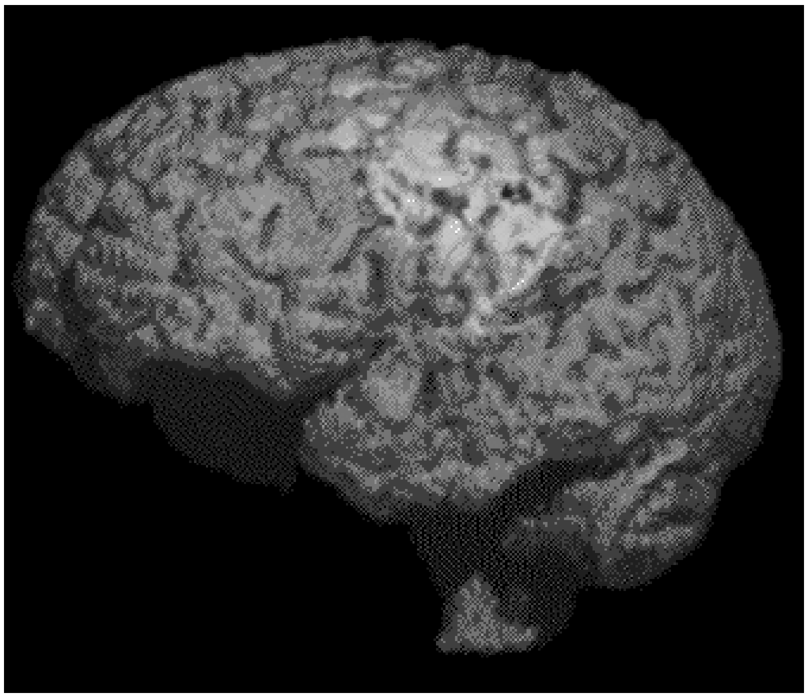
Improving Image "Resolution"

- Introduce prior information in weighting function [Dale&Sereno 93, Liu et al 98]
- Iteratively reweighted min norm - FOCUSS [Gorodnitzky&George94]
- Non-quadratic penalty function, e.g.

$$\min \|\boldsymbol{y}\|_p = \left|\sum_i \boldsymbol{y}_i^{\boldsymbol{p}}\right|^{\frac{1}{p}} \quad \text{subject to } |\boldsymbol{b} - \boldsymbol{A}\boldsymbol{y}| \leq \boldsymbol{e}$$

- [Jeffs&Leahy89 (p <1), Matsuura (p=1).

Bayesian Imaging



Phillips et al.

- Assume the image is probabilistic.
  - Gaussian prior, Gaussian noise: regularized min norm
- Non-Gaussian prior for ‘sparse” images [Phillips, Leahy & Mosher 97, Baillet & Garnero 98].

Bayesian Methods

- Statistical model:

$$p(\Theta / y) = \frac{p(y / \Theta)\, p(\Theta)}{p(y)}$$

- Unknowns Θ characterize solution:

  Θ an image

  - Gaussian prior, Gaussian noise: regularized min norm
  - Non-Gaussian prior for ‘sparse” images [Baillet & Garnero 98, Phillips,Leahy & Mosher 97].

  Θ a discrete set of sources

  - intersection of spheres with cortical surface [Schmidt & George, 99].

A Bayesian Model

- Stochastic model for source distribution based on assumption that activation is sparse and focal:
  - » Indicator process, x : binary process indicating which pixels are active
  - » Dynamic intensity process, $z(t)$: indicating intensity of active sites
  - » The dynamic source image is then $y(t)$=$x.*z(t)$

Bayes Theorem:

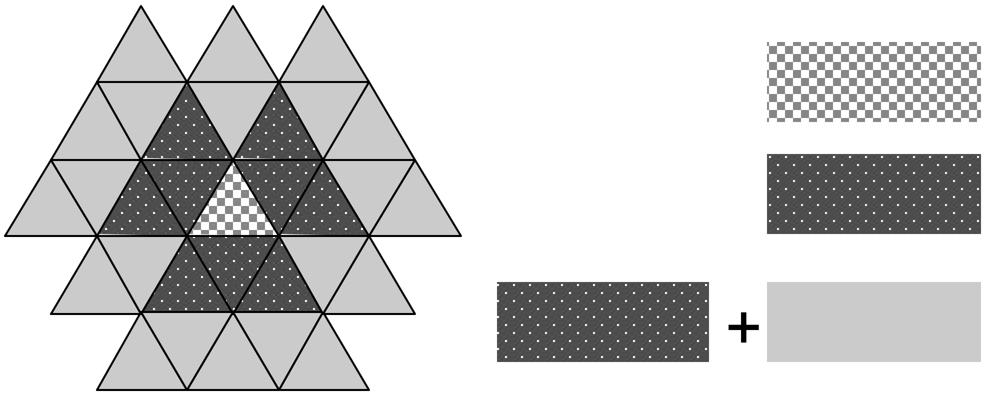
$$p(x,Z\,|\,B)=\frac{p(B\,|\,x,Z)\,p(x,Z)}{p(B)}$$

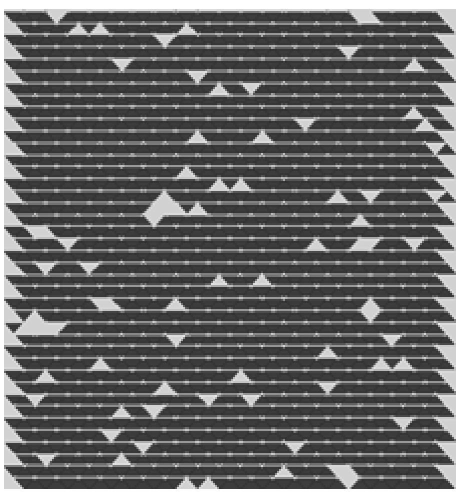
$$=\frac{p(B\,|\,x,Z)\,p(x)\,p(Z)}{p(B)}$$

- Assume indicator and intensity process are independent. Note: indicator process is time invariant - i.e. it indicates which sites are active at any time during the study.

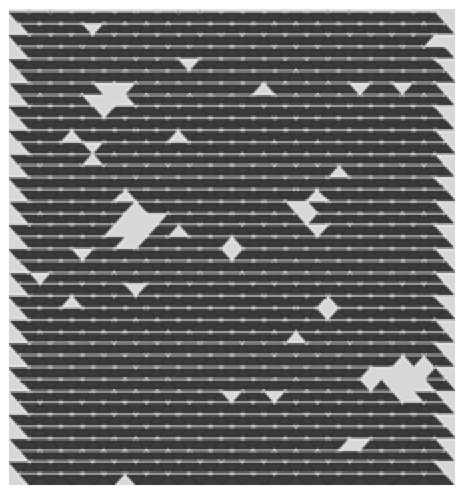
A Sparsness Prior

Triangular Tessellation

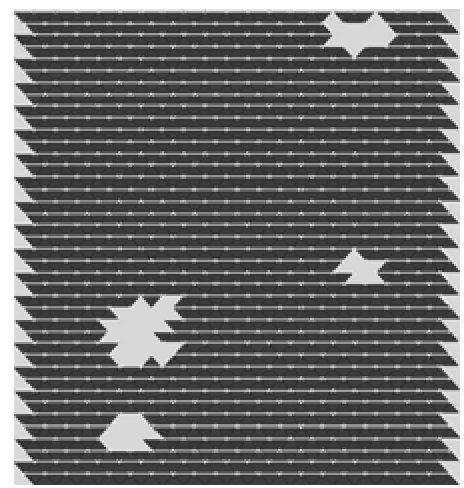




Q=1, α=0.2, β=0.20



Q=2, α=0.2, β=0.06

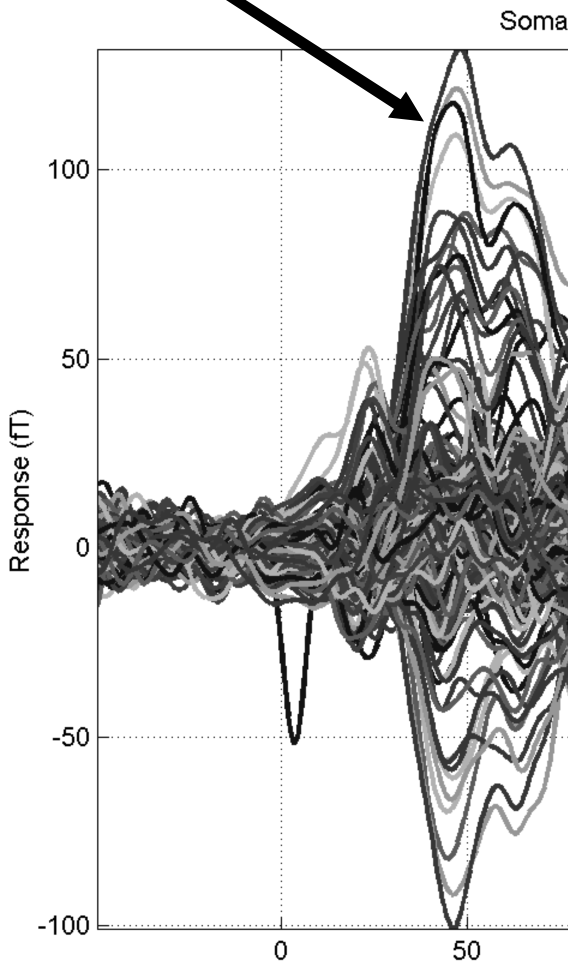


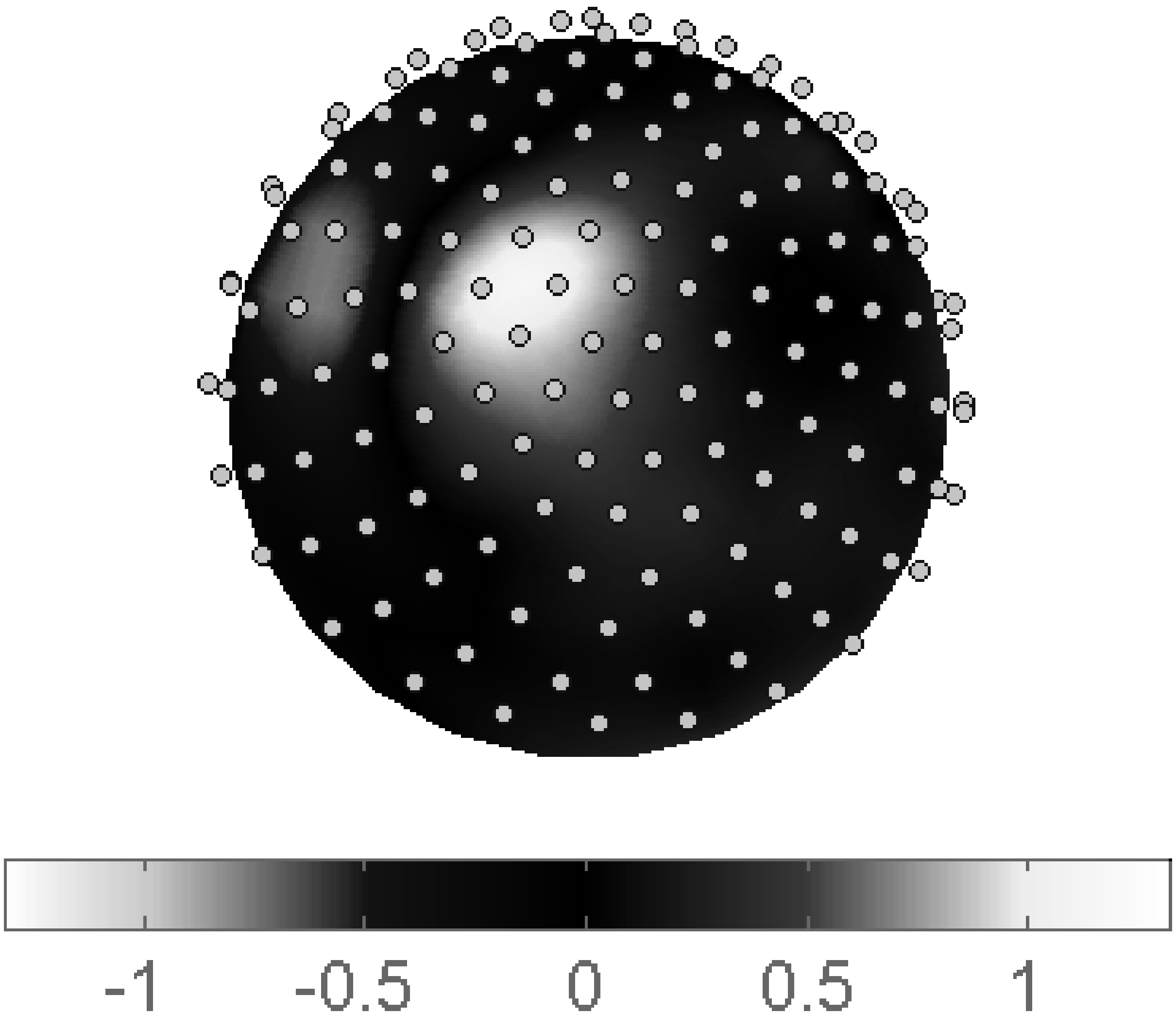
Q=3, α=0.2, β=0.017

Bayesian Estimation Schemes

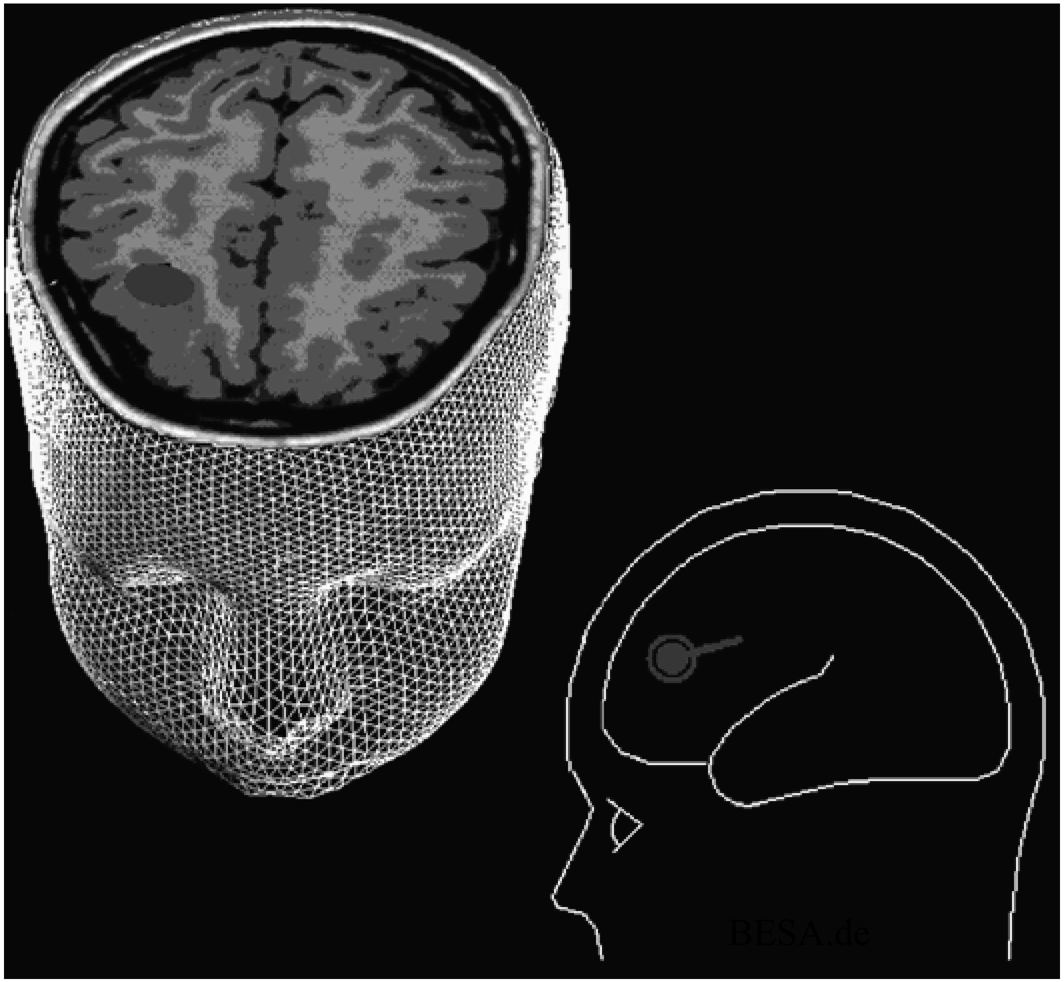
- Maximize function of posterior probability
  - 1. Joint-MAP for activation sites and amplitudes
  - 2. Marginalize out the amplitudes, MAP estimate of activation sites
  - 3. Maximum posterior marginal on each site - gives minimum error rate identification of activated sites
- Use mean-field annealing to handle binary variables identifying active sites
- <u>SHELVED</u>: At the end of the day, solution still strongly dependent on the prior, difficult end-user acceptance, long computation time.

Spatial Pattern Suggests Dipole





Dipolar Modeling



- 1950s 1st EEG dipolar modeling.
- Without anatomical images, interpretation of the dipolar solution was often quite limited.
- Today MRIs routinely collected, allowing better interpretations.

Inverse Methods: Parametric

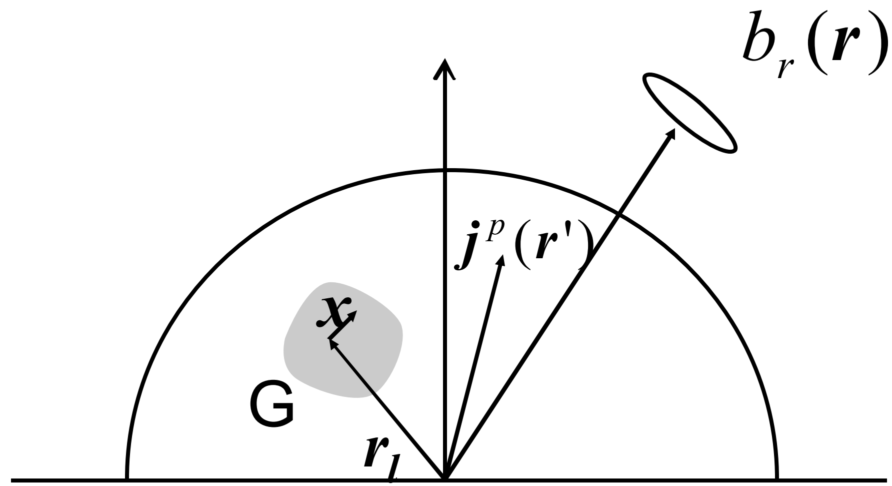
- Current dipole fitting
  - Assume few current dipoles, unknown locations and moments
  - Nonlinear least squares estimation problem - but now fewer parameters (5-6 per dipole)
  - Non-convex problem - local minima can be avoided using signal subspace (MUSIC) methods
- Key limitation
  - Can be difficult to interpret (dipoles not always in cortex)
  - Current dipoles may not adequately represent more distributed activation (model uncertainty).

Inverse Methods: Parametric

- Consider a “small” patch of activity on the cortical surface.
- Multipolar expansion collapses patch to an equivalent current dipole.
- Dipole not necessarily in the cortex.

Multipolar Source Modeling

- Taylor series expansion of $|\boldsymbol{r}-\boldsymbol{r}'|^3$ about $\boldsymbol{r}_l$ for source confined to region G
- 1^{st}-order multipole: dipole + quadrupole
- Max rank of 11, (lower for sphere, radial orientation)



$$\boldsymbol{M}(\boldsymbol{r}) = \boldsymbol{r} \times \boldsymbol{j}^p(\boldsymbol{r})$$

$$b_r(\boldsymbol{r}) = \frac{m_0}{4p} \frac{\boldsymbol{r}}{r|\boldsymbol{r}-\boldsymbol{r}_l|^3} \cdot \int_G \left(\boldsymbol{M}(\boldsymbol{r}_l+\boldsymbol{x}) + \frac{3\boldsymbol{M}(\boldsymbol{r}_l+\boldsymbol{x})}{|\boldsymbol{r}-\boldsymbol{r}_l|^2} x \cdot (\boldsymbol{r}-\boldsymbol{r}_l) + \dots \right) d\boldsymbol{x}$$

Multipolar Current Patterns

- Planar square grid of dipoles
- SVD (PCA) of model matrix
- Orthogonal patterns ranked by singular values

Multipolar Modeling

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Phys. Med. Biol. **47** (2002) 1–32 PII: S0031-9155(02)27491-6

On MEG forward modelling using multipolar expansions

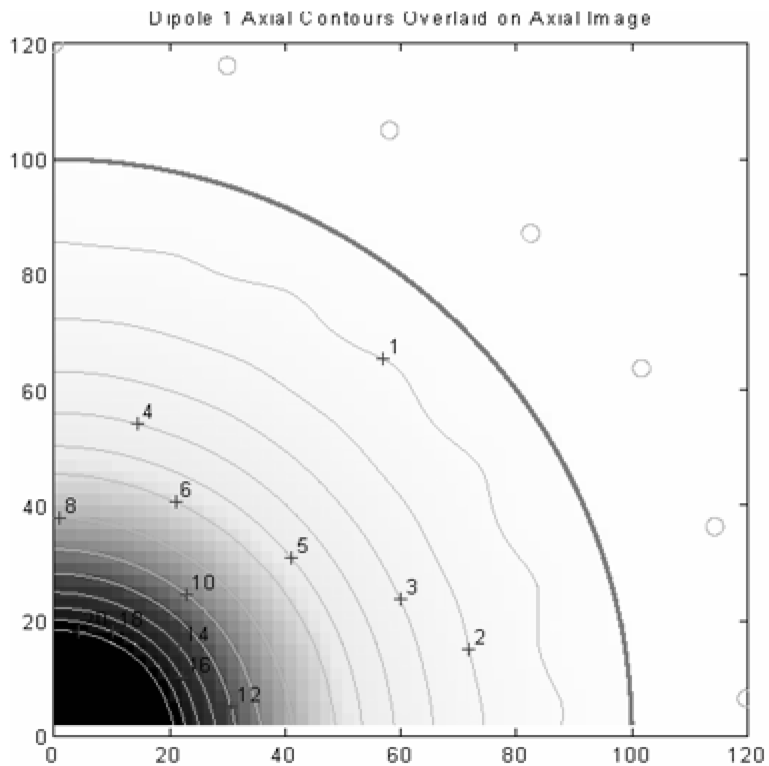
K Jerbi[1,3], J C Mosher[2], S Baillet[3] and R M Leahy[1]

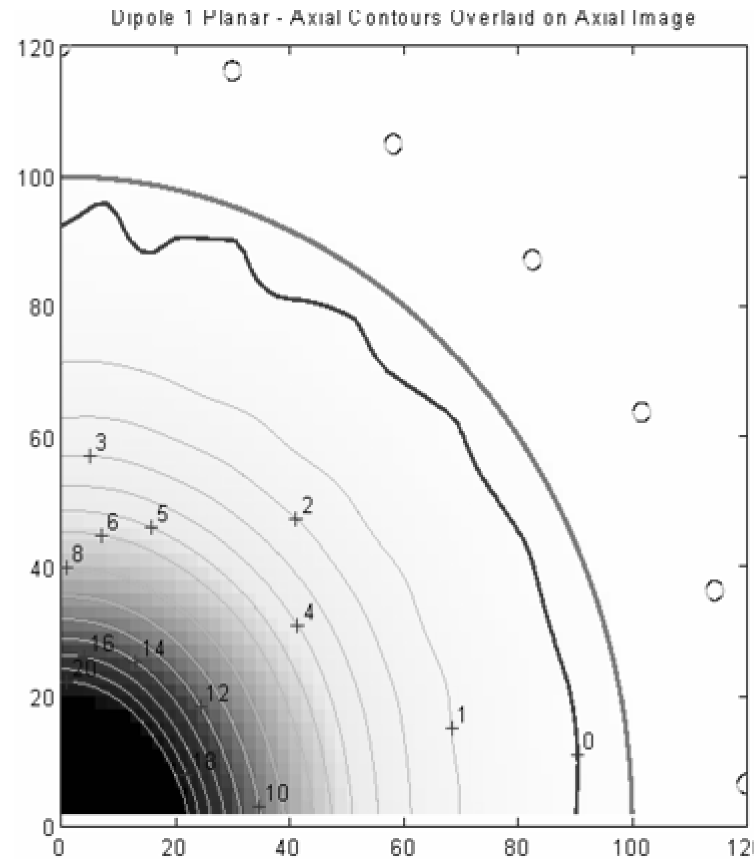
[1] Signal and Image Processing Institute, University of Southern California, Los Angeles, CA, USA
[2] Los Alamos National Laboratory, Los Alamos, NM, USA
[3] Cognitive Neuroscience and Brain Imaging Laboratory, Hôpital de la Salpêtière, CNRS, Paris, France

Nonlinear Least-Squares

- Separate nonlinear location parameters from the quasilinear orientation and linear amplitude parameters (Golub and Pereya 1973).
- May need several dipoles.
- Nonconvex error function comprising possibly dozens of parameters.
- Need to consider temporal information to simplify problem.

Dipolar Accuracy Studies Cramer-Rao Lower Bounds





- Axial Gradiometer
- Planar difference

Single Time Slice Limitations

- Consider hundreds of sensors
  - limit -> Hilbert space (see geophysical inverse models)
- Forbidden zone limits rank of space ~50
- "Model" parameters should not exceed ~10% of independent observations
  - Greater than 1/3, you have a transform (overmodeling)
- Each dipole has three nonlinear, 2-3 linear parameters
- **Three – four dipoles maximum. Emphasize: Single Time Slice.**

Temporal Models

- Static data have the same limitations as geophysical data:
  - Focal models suitable for mostly isolated sources.
  - Multiple adjacent sources difficult to model.
- Unlike the Earth, brain has richness of temporal diversity to distinguish sources.
- Emphasize the "quasi" in quasistatic EM.

Data Covariance

- Noise statistics:

$$E(\boldsymbol{n}) = \boldsymbol{0}, \quad E(\boldsymbol{n}\boldsymbol{n}') = \boldsymbol{C}_n$$

- Data statistics:

$$E(\boldsymbol{d}) = \boldsymbol{G}\boldsymbol{j}, \quad E(\boldsymbol{d}\boldsymbol{d}') = \boldsymbol{G}\boldsymbol{C}_j\boldsymbol{G}^T + \boldsymbol{C}_n$$

  – (assume noise and moments independent)

- We need (once again) to make some assumptions about the covariance (correlation) of the dipole moments.

Data Covariance Estimation

- Need many time slices

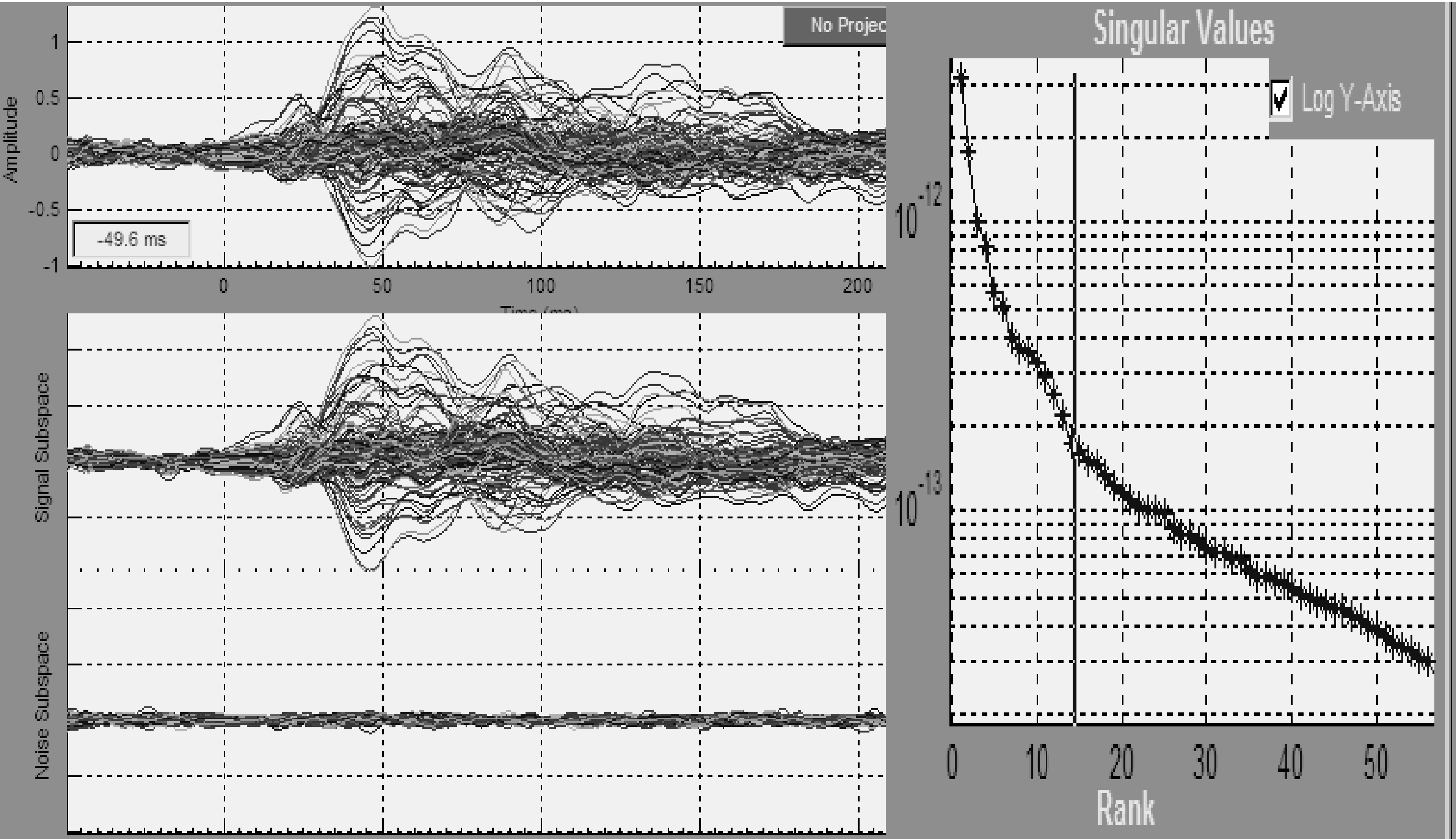
$$\boldsymbol{D} \equiv [\boldsymbol{d}(1), \boldsymbol{d}(2), \cdots, \boldsymbol{d}(N)]$$

- Estimate as sample covariance matrix

$$\hat{\boldsymbol{C}}_{\boldsymbol{d}} = \frac{1}{N-1} \boldsymbol{D}\boldsymbol{D}^T$$

- Note: For low SNR, $\boldsymbol{C}_{\boldsymbol{d}} \cong \boldsymbol{C}_{\boldsymbol{n}}$

Data Matrices are Low Rank!



Manifold Model

- We can reduce the data matrix to a relatively low rank basis set.

$$\boldsymbol{D} \cong \boldsymbol{U}_s \sum_s \boldsymbol{V}_s^T$$

- We can build a model from a handful of dipoles.

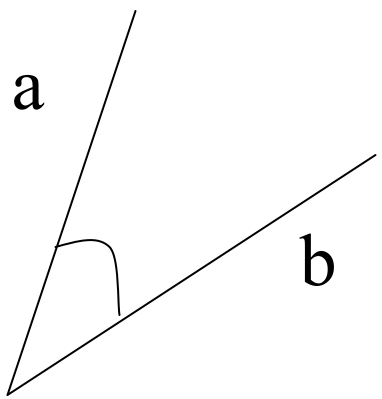
$$\boldsymbol{D} \cong [\boldsymbol{G}_1, \boldsymbol{G}_2, \cdots, \boldsymbol{G}_p]\boldsymbol{J}^T$$

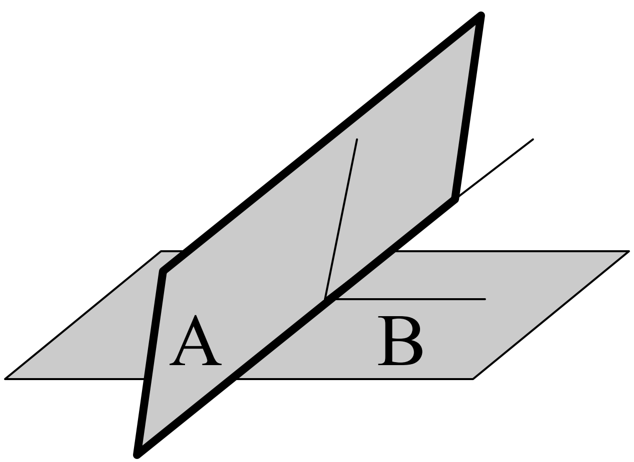
- Set of dipoles represents a **manifold**.

Subspace Comparisons

- SVD (or PCA) has extracted a "narrow" signal subspace from the data. $\boldsymbol{U}_s$
- Low-order dipole model generates a "narrow" model subspace. $[\boldsymbol{G}_1, \boldsymbol{G}_2, \cdots, \boldsymbol{G}_p]$
- If we assume time series are linearly independent, then each $\mathbf{G_i}$ lies in the space spanned by $\mathbf{U_s}$

Subspace Correlations





- Also known as:
  - Canonical Correlations
  - Principal Angles
- 1-D lines, angle between two lines
  - $a^T/|a| * b/|b|$
  - $\mathrm{orth}(a)^T * \mathrm{orth}(b)$
- 2-D Planes in 3-D
  - First angle always zero
  - Second angle gives "distance"
- N-D hyperplanes
  - $\mathrm{svd}(\mathrm{orth}(A)^T * \mathrm{orth}(B))$

Comparison Steps

- Singular value decomposition (SVD) of the data matrix

$$\boldsymbol{U}\boldsymbol{S}\boldsymbol{V}^T = \boldsymbol{D}$$

- Pick out signal subspace (significant singular values)

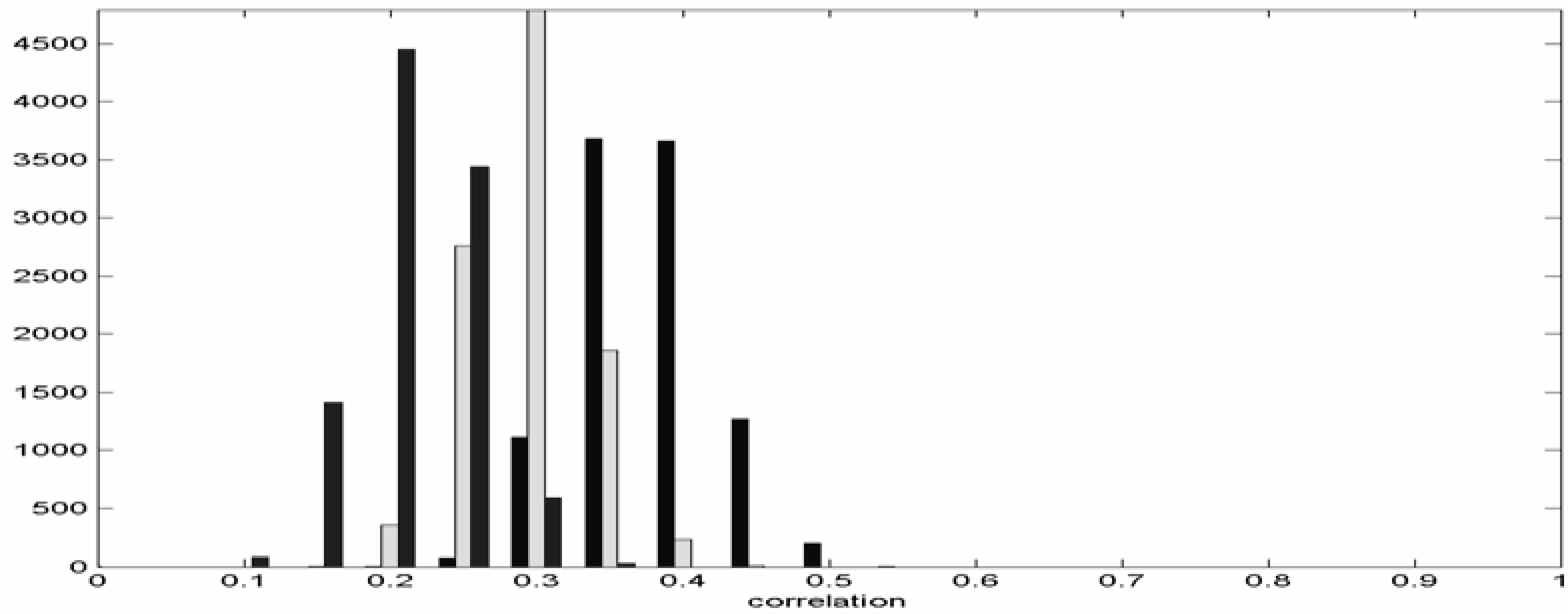
$$\boldsymbol{U} \equiv [\boldsymbol{U}_d \ \overline{\boldsymbol{U}}_d]$$

- Orthogonalize dipole model, $\boldsymbol{U}_{\boldsymbol{G1}}$

- SVD of $(\boldsymbol{U}_{\boldsymbol{G}1}^T \boldsymbol{U}_{\boldsymbol{d}})$ yields correlations.

Subspace Intersections

- Consider 150 dimensional space
- Consider random rank 15 subspace vs. random rank 3 subspace



Process

- Grid the putative source volume and form dipoles at each point.
- Compare the correlation between the dipolar model and the signal subspace for all grid points.
- From the best grid point, maximize the correlation using a conventional nonlinear optimizer.

MUSIC

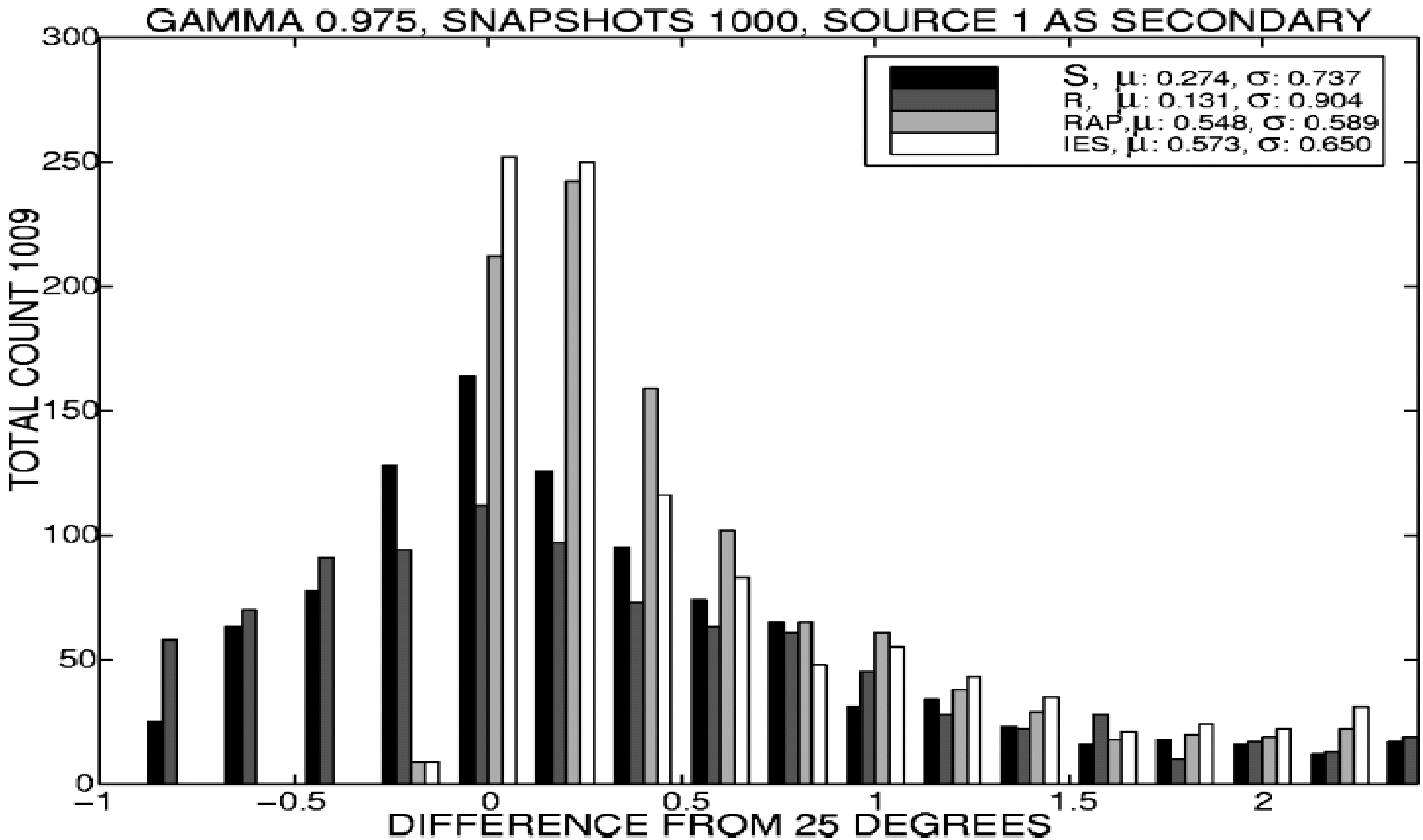
- Multiple Signal Characterization (MUSIC) introduced by R. Schmidt in 1979 for RADAR and SONAR.
- Adapted by Mosher et al. 1992 for temporally diverse neural signals
  - "classical MUSIC."
- Enhanced 1999 using Recursively Applied Projections for more automated processing and general models
  - "RAP-MUSIC."
- Generally considered a "scanning metric" since single dipolar sources can be extracted in simple 3-D scans of the brain.

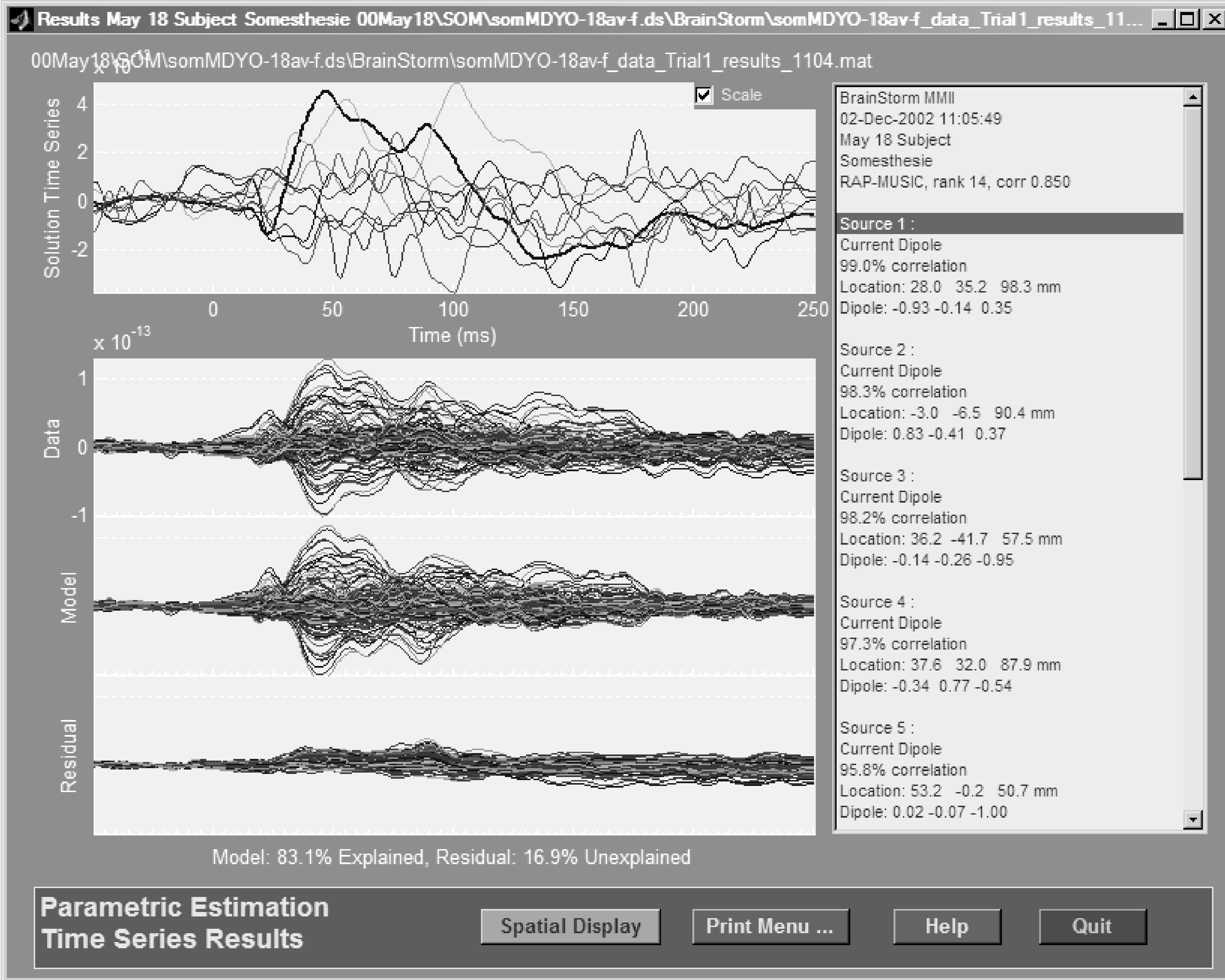
RAP-MUSIC

- Having found the best correlation between a model subspace and a signal subspace, how do we search for the 2nd peak? (Peak-picking problem in multiple dimensions.)

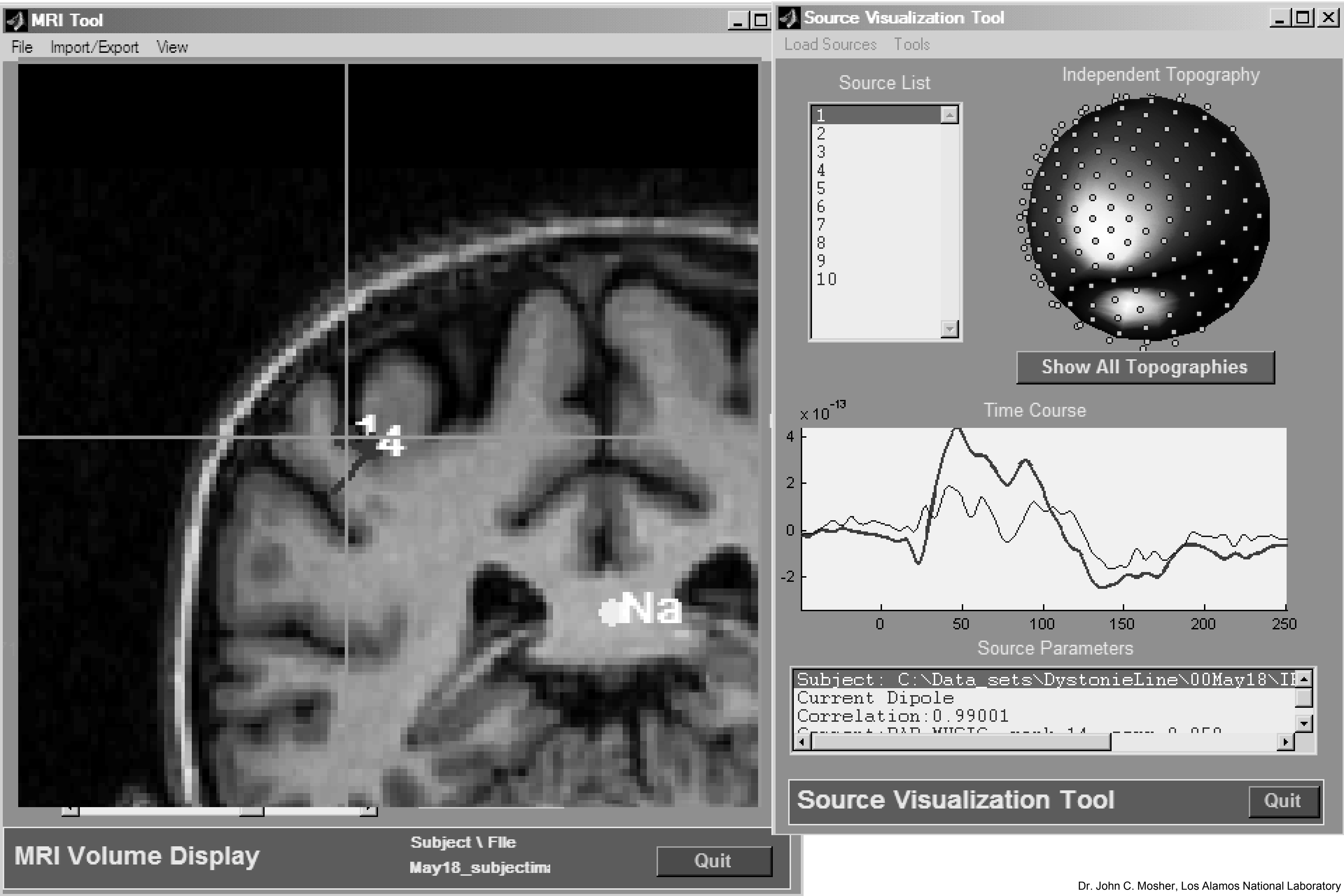
- Solution: Project data and models away from the previous solution and maximize in the lower dimensional space.

RAP-Slight bias, smaller variance



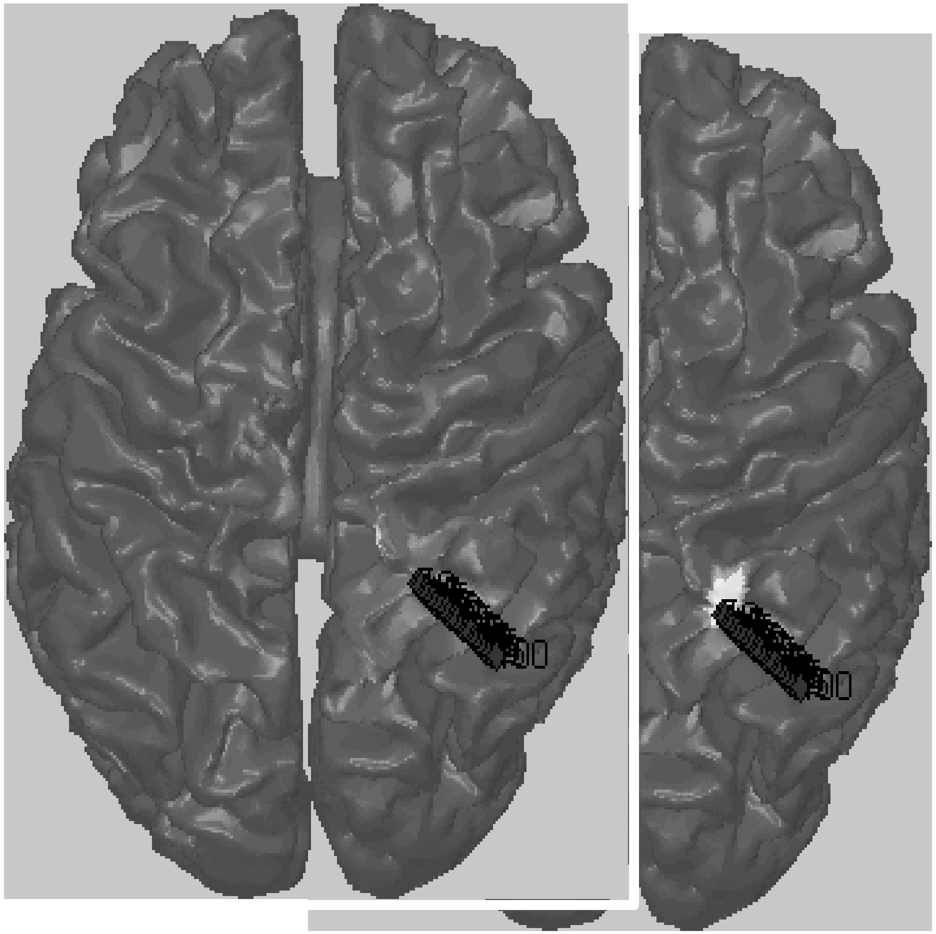


Results May 18 Subject Somesthesie 00May18\SOM\somMDYO-18av-f.ds\BrainStorm\somMDYO-18av-f_data_Trial1_results_11...
00May18\SOM\somMDYO-18av-f.ds\BrainStorm\somMDYO-18av-f_data_Trial1_results_1104.mat
Scale
Solution Time Series
Time (ms)
Data
Model
Residual
BrainStorm MMII
02-Dec-2002 11:05:49
May 18 Subject
Somesthesie
RAP-MUSIC, rank 14, corr 0.850
Source 1 :
Current Dipole
99.0% correlation
Location: 28.0 35.2 98.3 mm
Dipole: -0.93 -0.14 0.35
Source 2 :
Current Dipole
98.3% correlation
Location: -3.0 -6.5 90.4 mm
Dipole: 0.83 -0.41 0.37
Source 3 :
Current Dipole
98.2% correlation
Location: 36.2 -41.7 57.5 mm
Dipole: -0.14 -0.26 -0.95
Source 4 :
Current Dipole
97.3% correlation
Location: 37.6 32.0 87.9 mm
Dipole: -0.34 0.77 -0.54
Source 5 :
Current Dipole
95.8% correlation
Location: 53.2 -0.2 50.7 mm
Dipole: 0.02 -0.07 -1.00
Model: 83.1% Explained, Residual: 16.9% Unexplained
Parametric Estimation
Time Series Results
Spatial Display
Print Menu ...
Help
Quit



Dr. John C. Mosher, Los Alamos National Laboratory

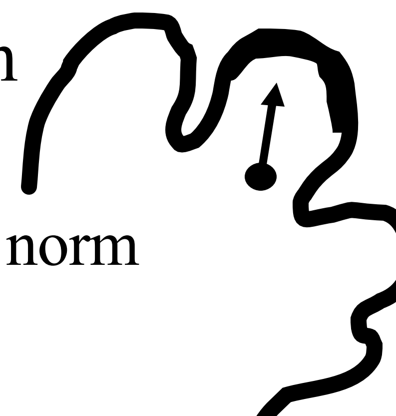
Cortical Remapping



Min-norm

Region Growing

- Remap sources onto cortex: find a local patch of cortex whose activation explains the magnetic field associated with each source:
  - weighted min norm imaging
  - seeded region growing



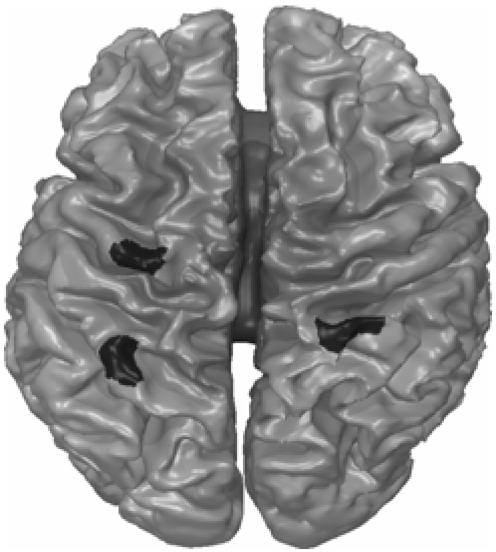
BrainStorm

Multipolar Source Imaging

Preprocessing
averaging
noise removal
channel rejection
select time window

Fit multipolar sources to data:
current dipoles
1st order multipoles

Re-map each source onto cerebral cortex
- display activation sites and associated time series



Outline

- "Imaging" vs. "Modeling" of data
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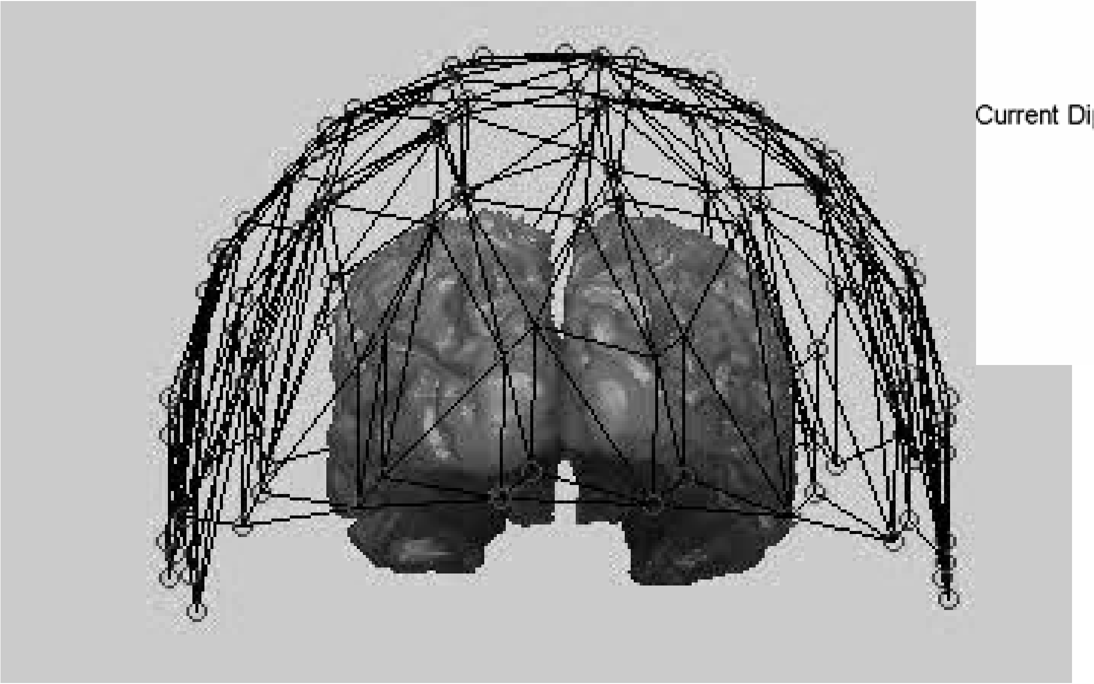
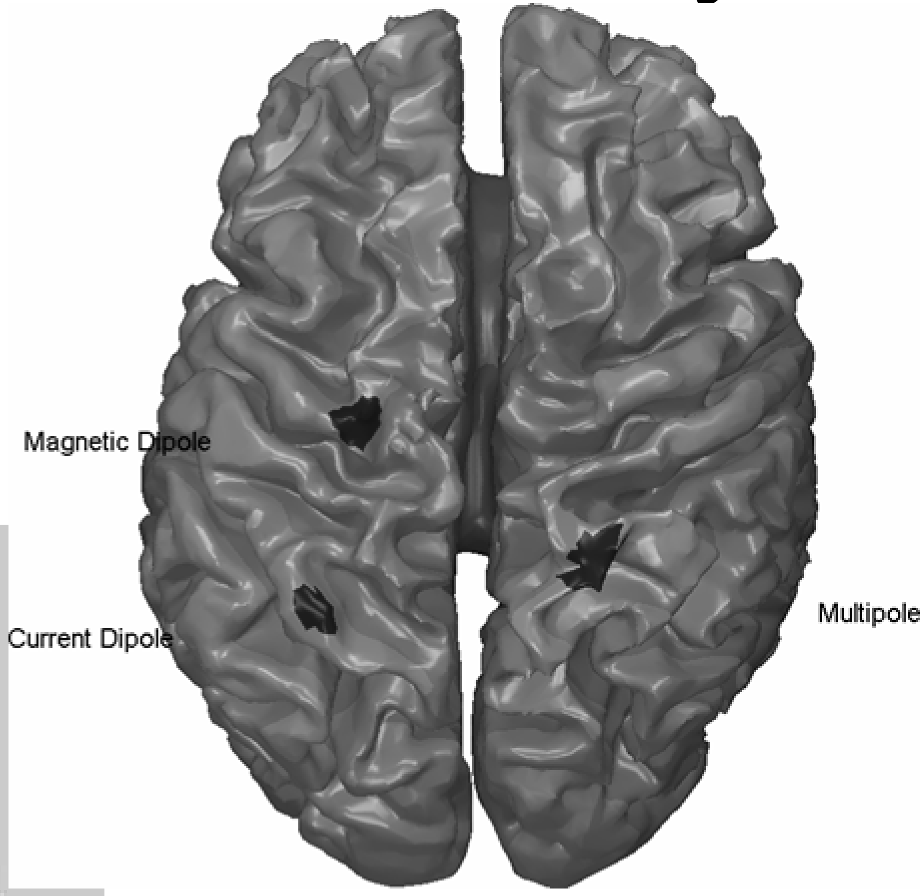
- Inverse Modeling
- Simulated and Experimental Results

Simulation Study

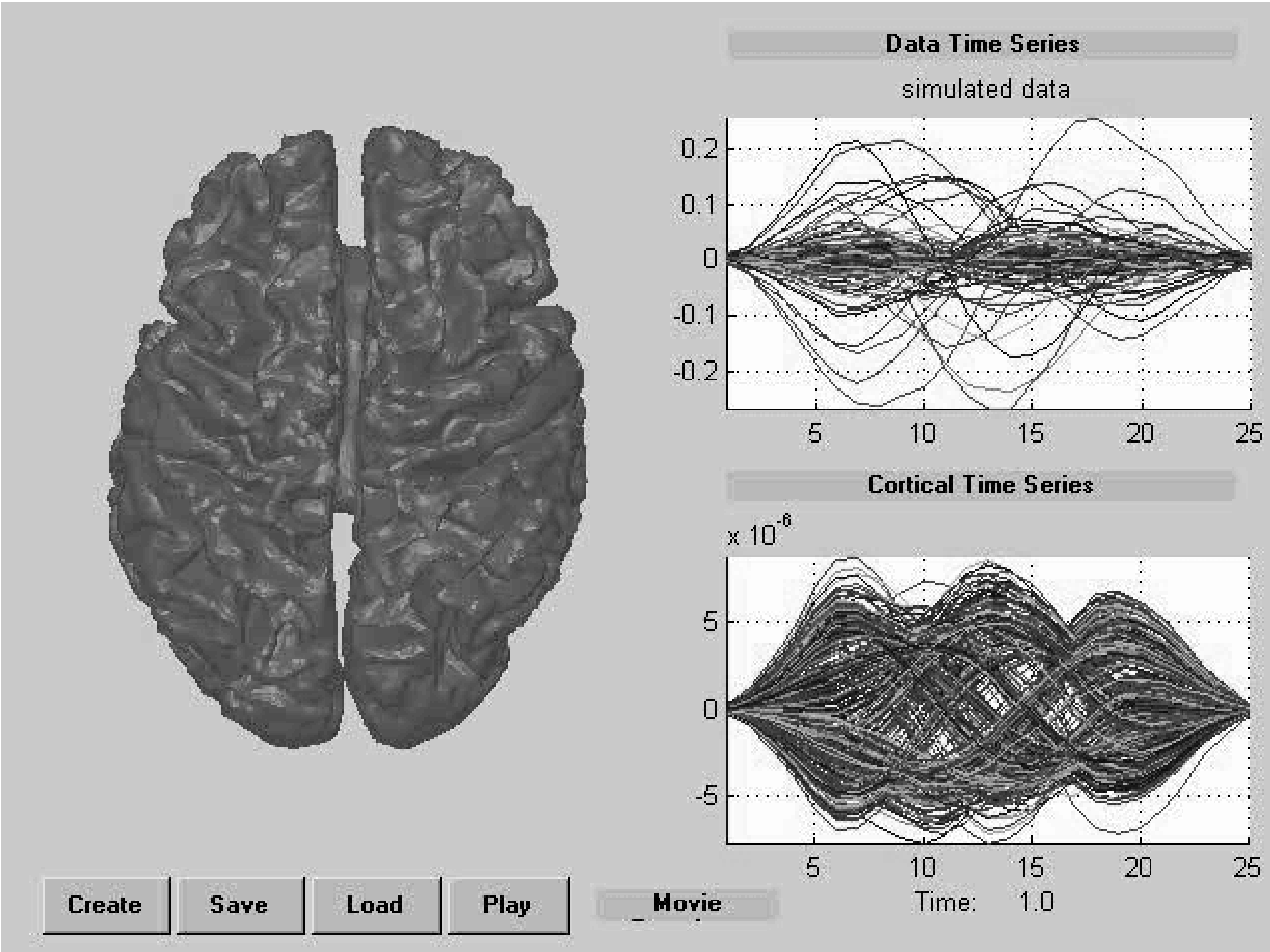
- 122 planar gradiometers
- 100k cortical triangles
- 3 distributed sources





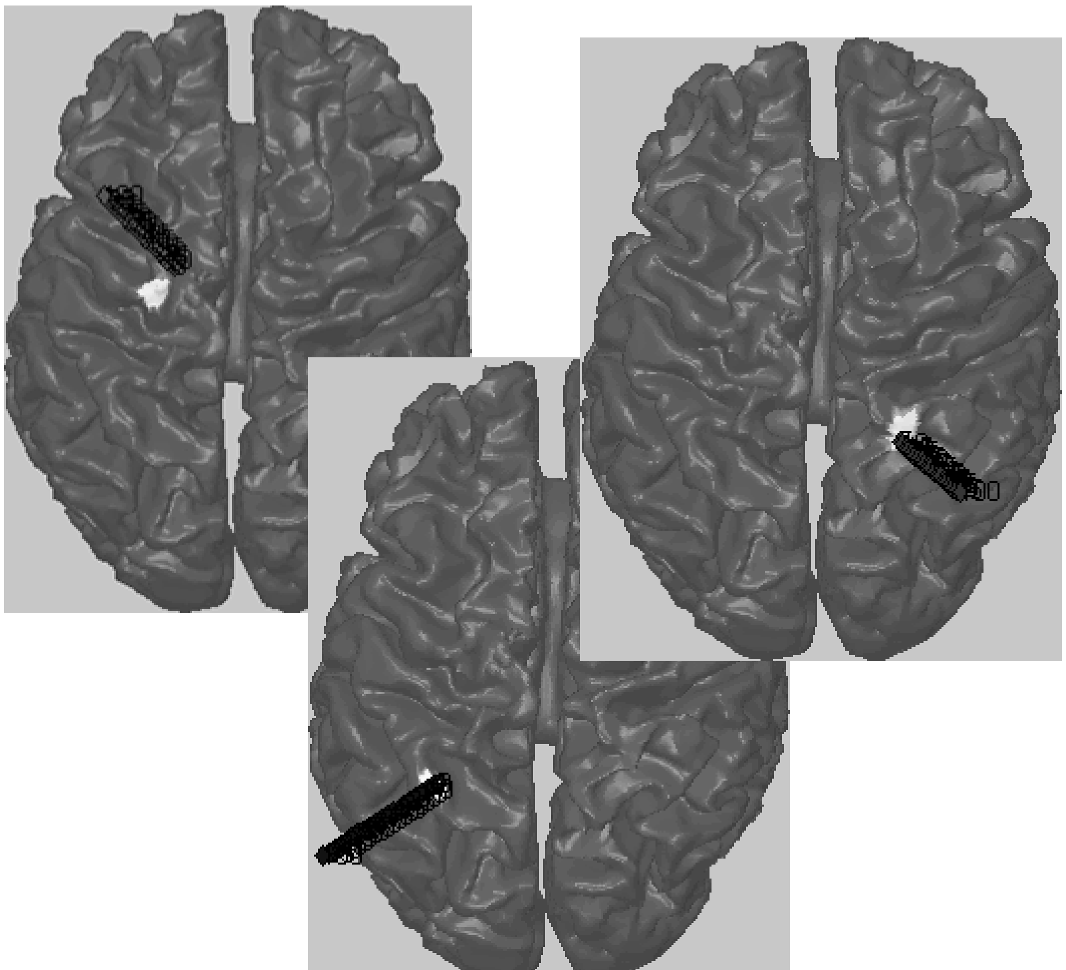
BrainStorm

Minimum Norm Solution



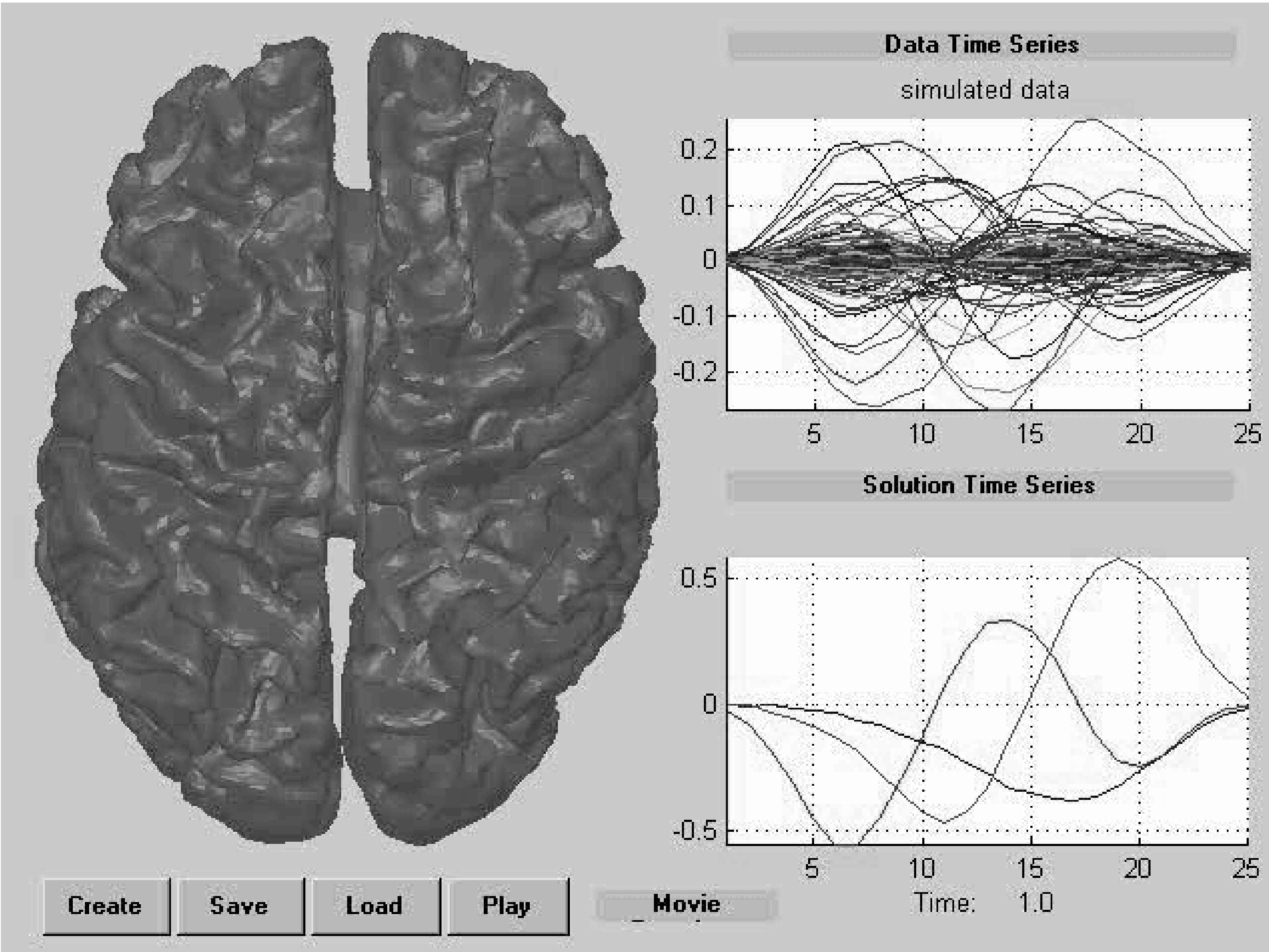
BrainStorm

RAP MUSIC Solutions



- Sources found:
- 1) current dipole
- 2) magnetic dipole
- 3) Multipole
- Seeded region growing around source solution.

Constrained Topographies

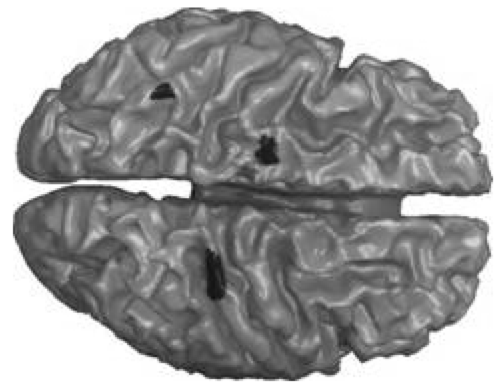


- RAP-MUSIC for solution approach.
- Various multipolar models as source.
- Seeded region growing.

BrainStorm

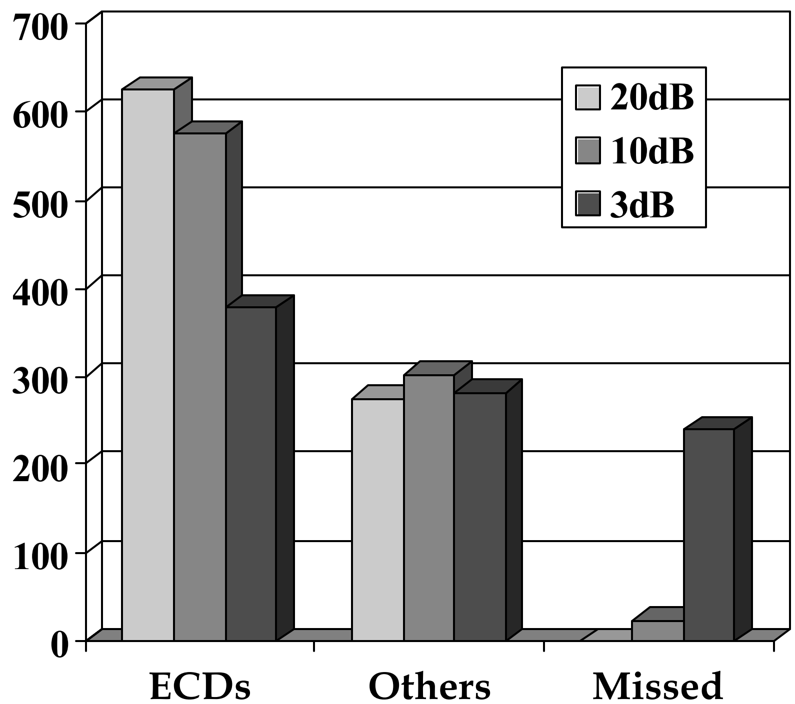
Monte Carlo Simulation

- 3 focal sources generated on human cortex (230,000 triangles). Each source 200mm^2 monophasic or 2x200mm^2 (50% overlap) biphasic patch randomly positioned on upper cerebral cortex.

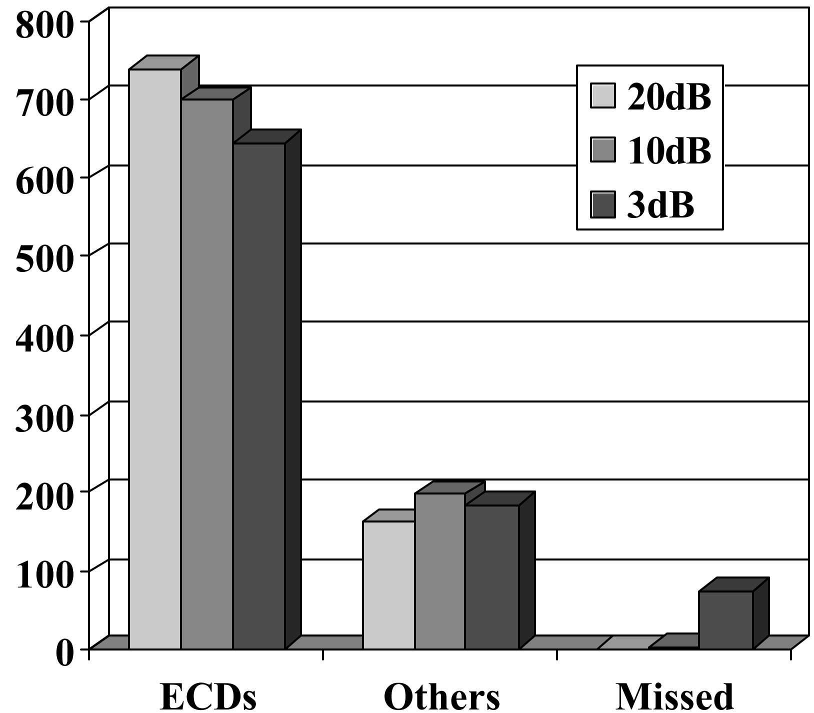


- RAP MUSIC - Monte Carlo investigation (3,600 source configurations) of effects of correlation threshold and SNR on source localization.

Monte Carlo Results



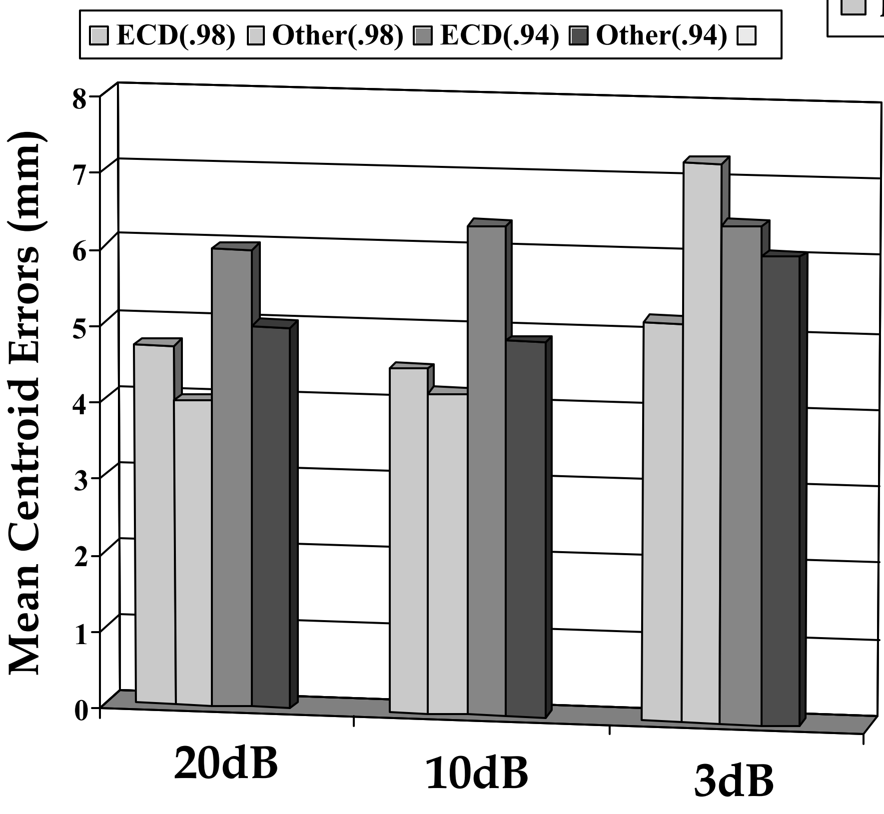
Correlation threshold: 98%

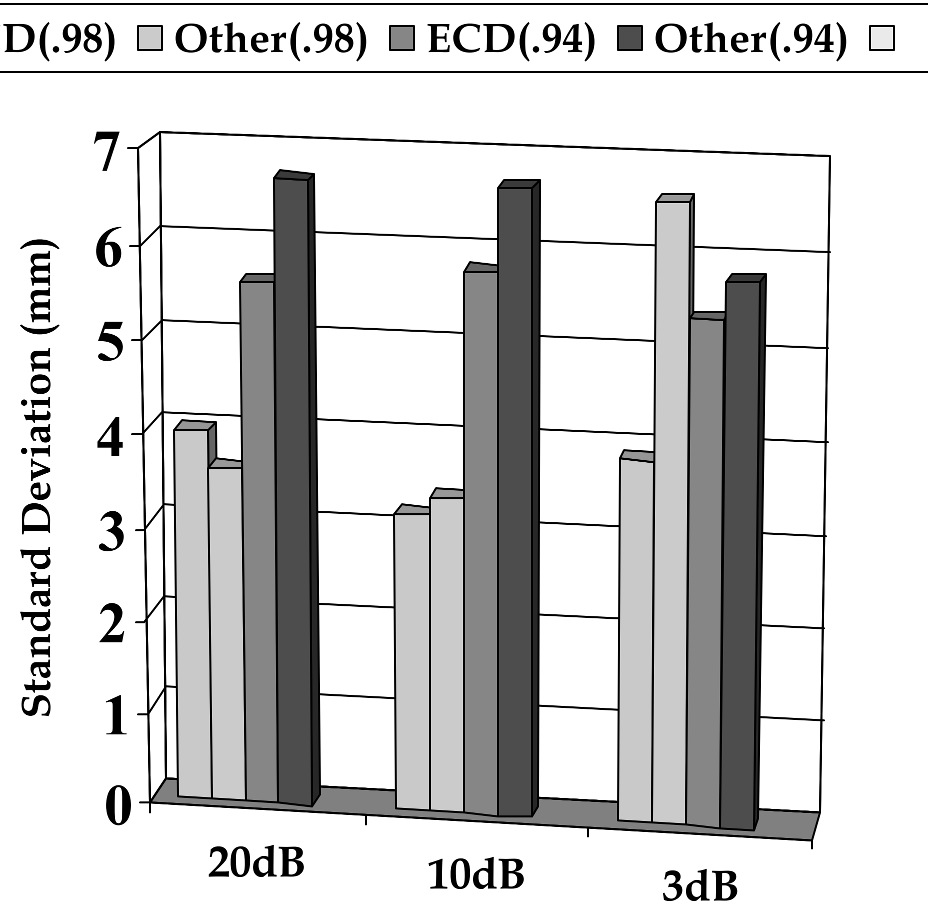


Correlation threshold: 94%

ECD = equivalent current dipole
Others = magnetic dipole or first order multipole

Localization Errors

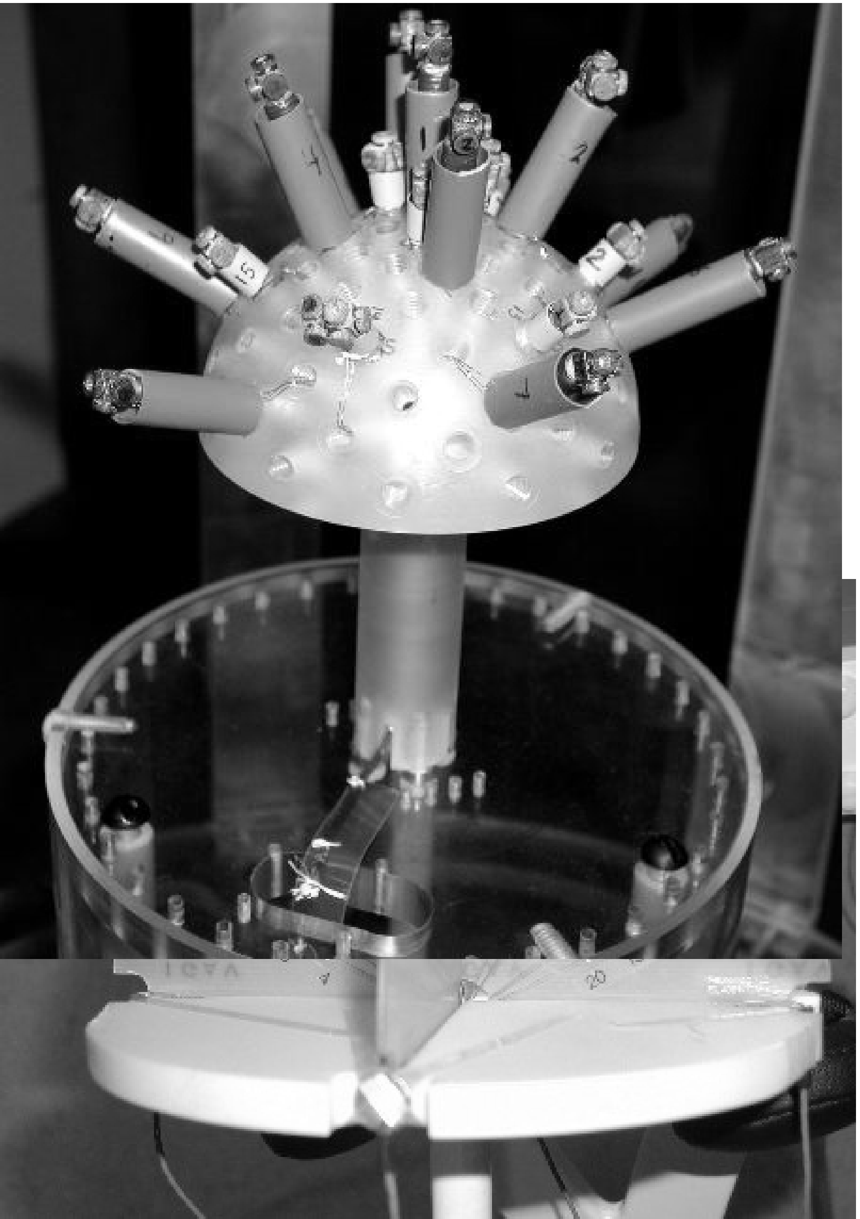




ECD = equivalent current dipole

Others = magnetic dipole or first order multipole

"Dry" Calibration Phantoms

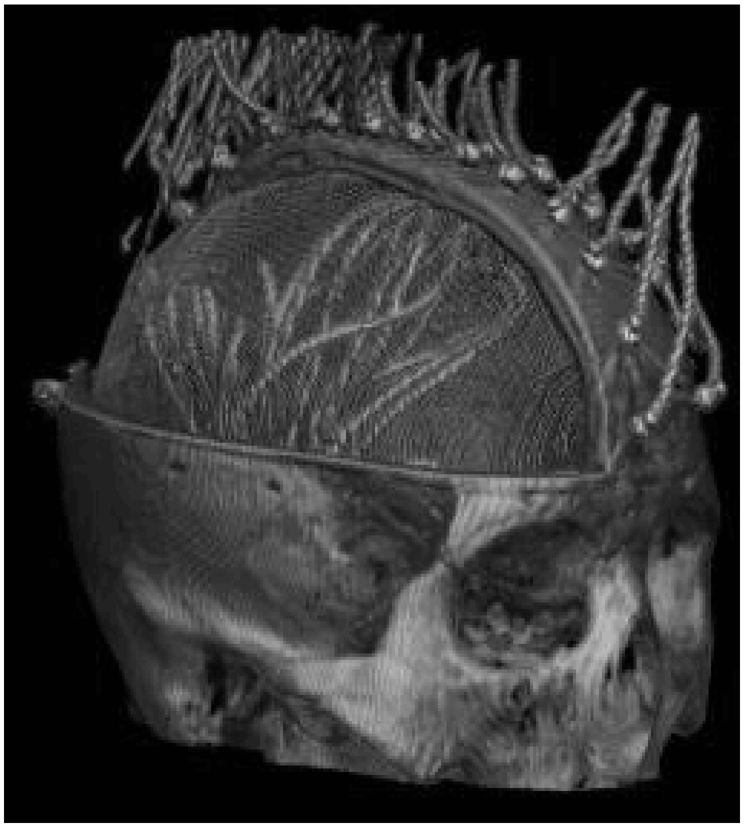


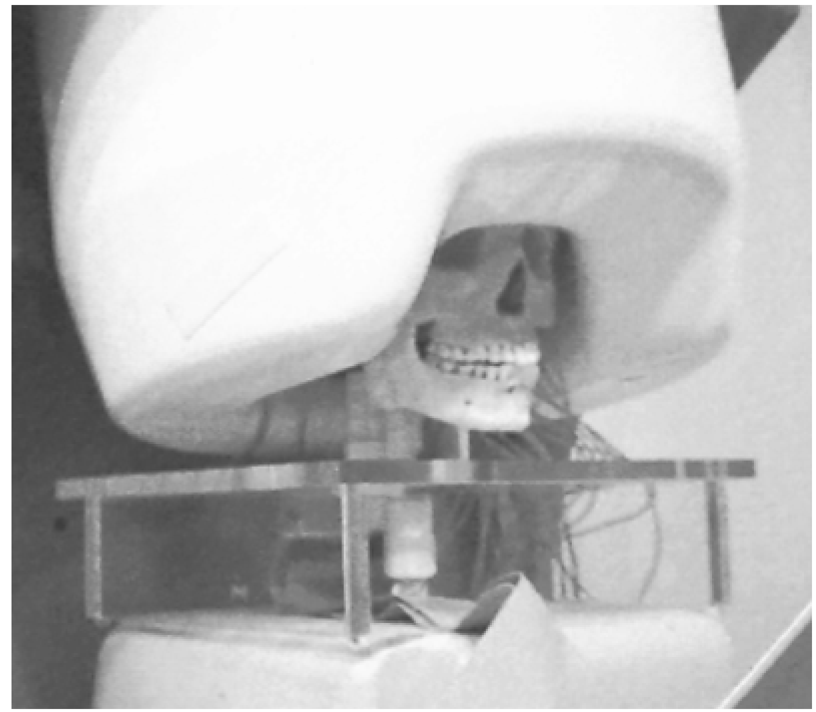
- At LANL, three-axis circular magnetic dipoles.
- From Neuromag, triangular-shaped magnetic dipoles virtually identical to current dipoles.

Human Skull Phantom

32 coaxial optically-isolated current dipole sources

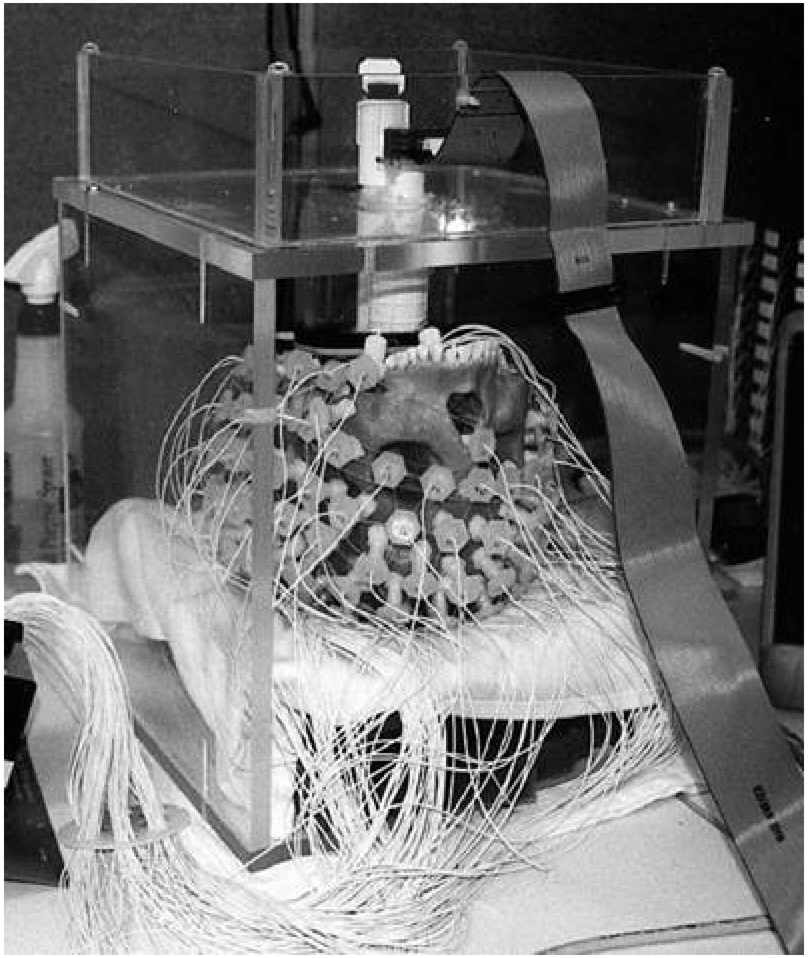
EEG and MEG Compatible





Ground truth from CT scan

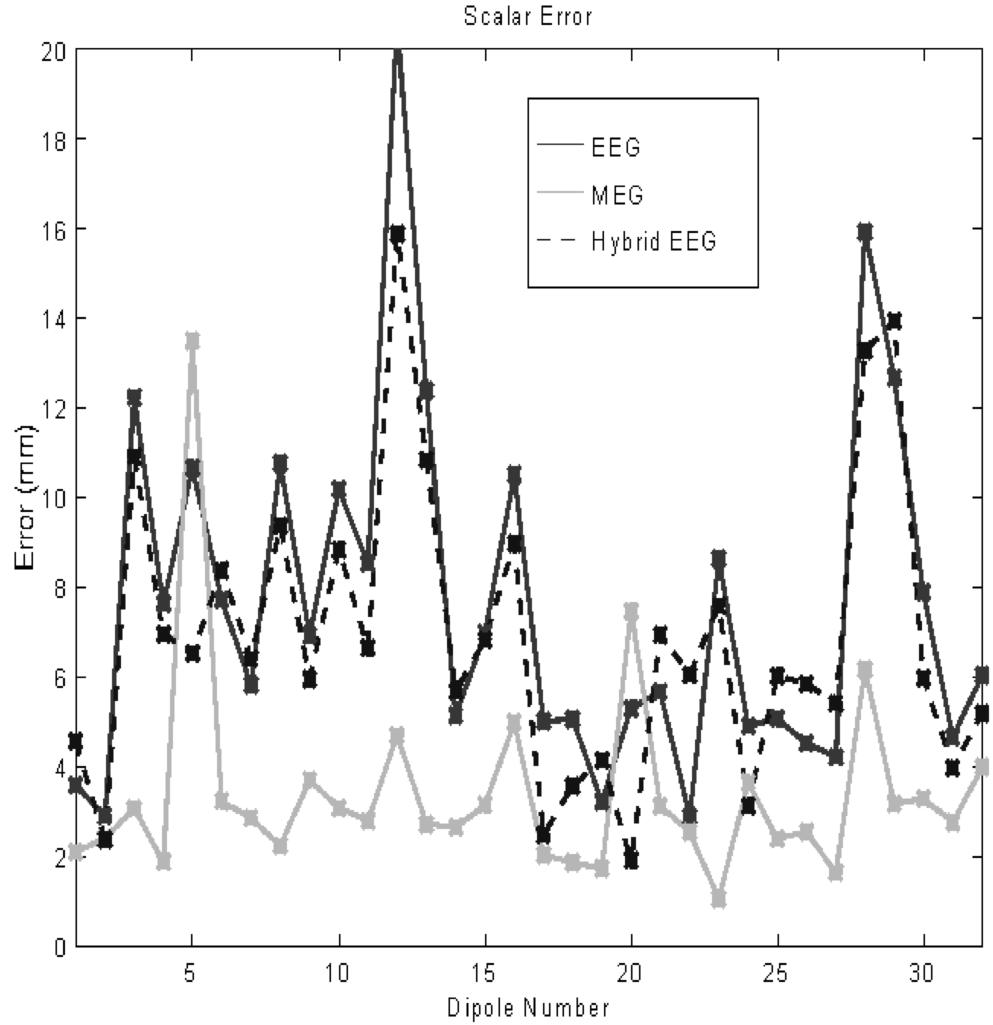
EEG Phantom Studies



- Colleagues at EGI, Incorporated, Eugene, OR.
- Novel 128 channel EEG array, placed simultaneously like a hairnet.
- USC Human skull phantom tested on EGI machines.

Phantom Localization Errors

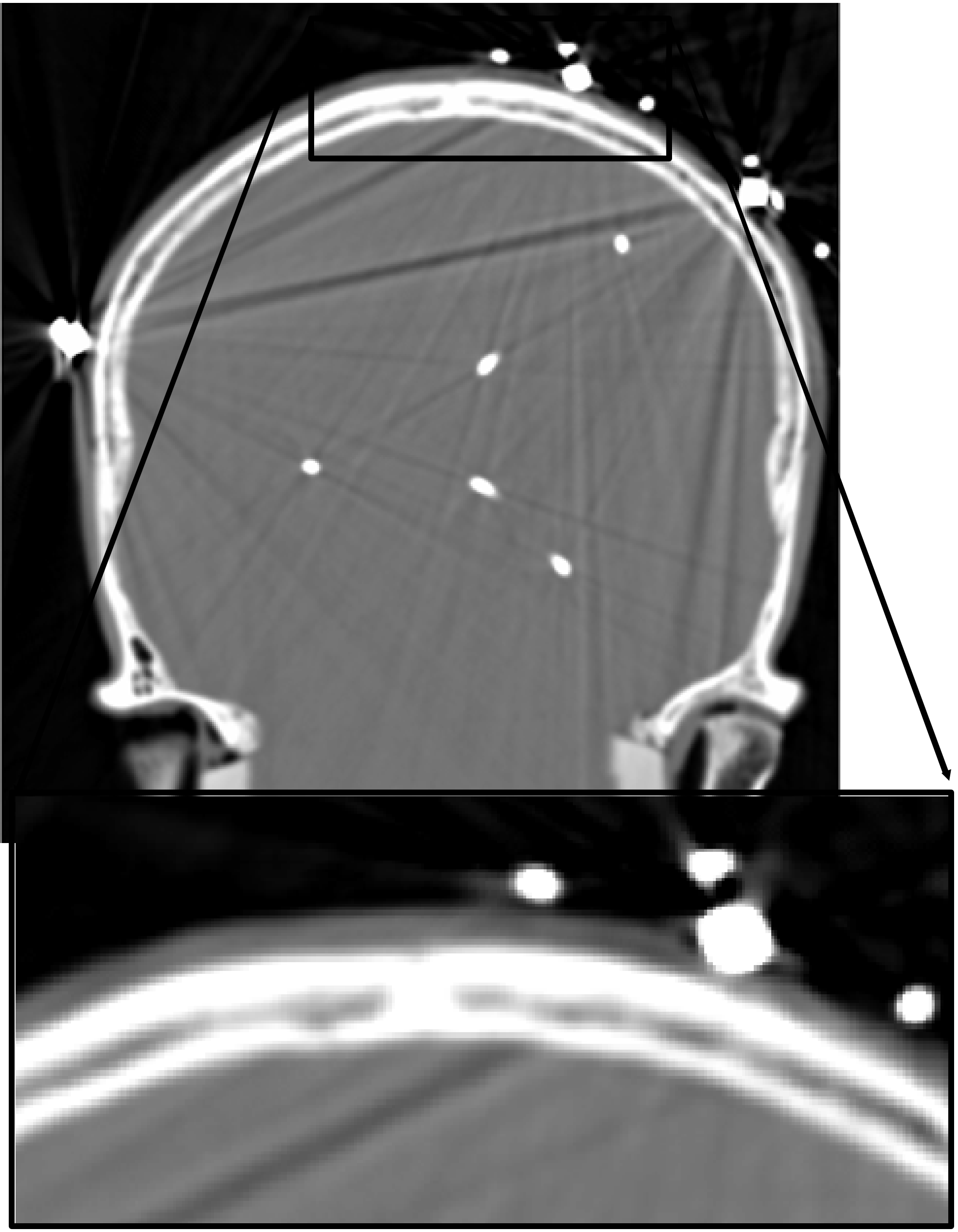
- Sources fit using R-MUSIC, spherical and realistic BEM forward models
- Average error for 32 dipoles using spherical head model: 4.1mm
- Average error for 32 dipoles using BEM head model: 3.4mm
- EEG: 2x greater error



Localization error (mm)

Dipole Number.

EEG: Uncertain Skull Model

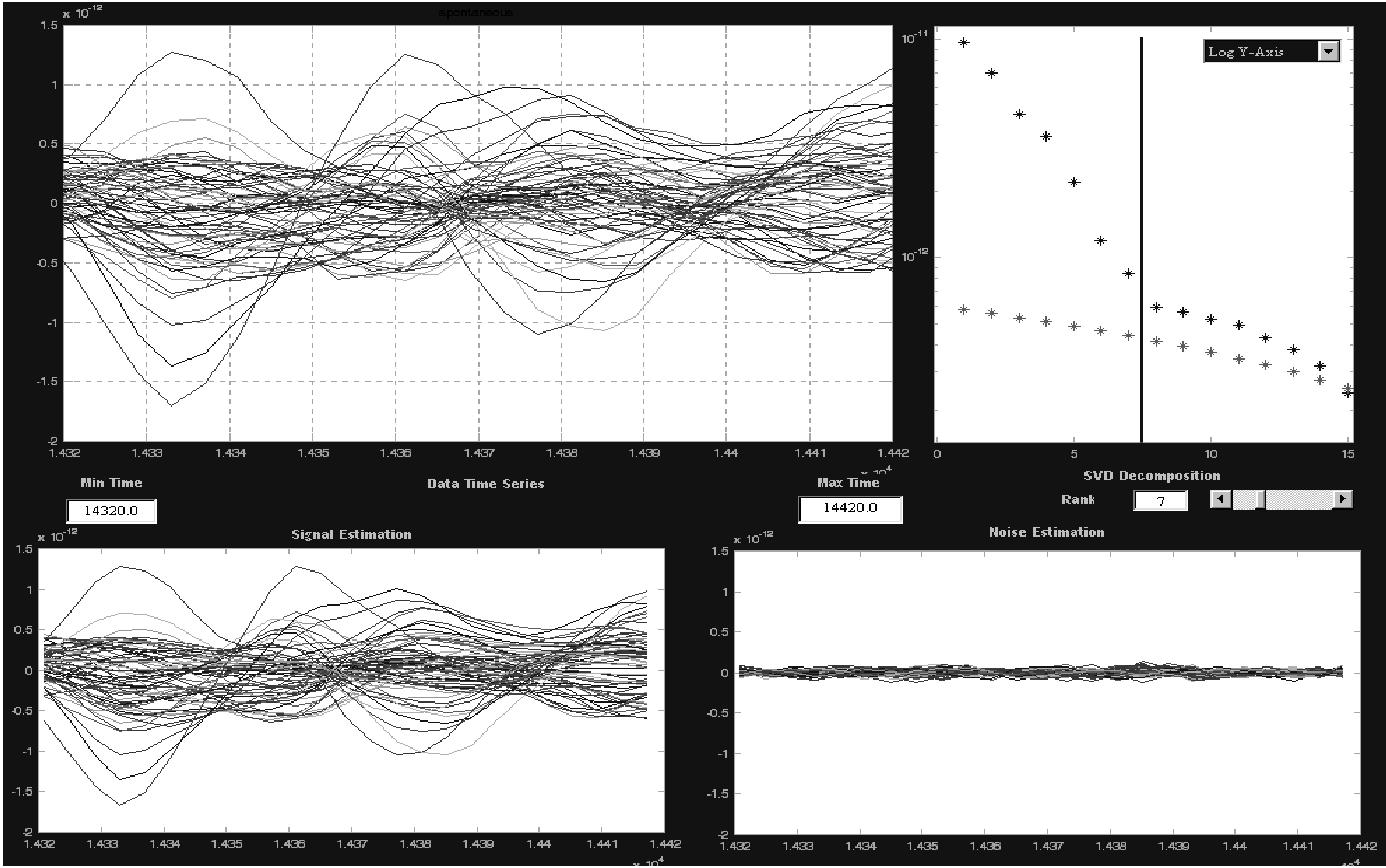


- Simulated differences in noise, array coverage, array density.
- Experimental errors much larger than theory for EEG.
- Supposition is the imprecision in modeling the diploic space.

Epileptic Spike Data

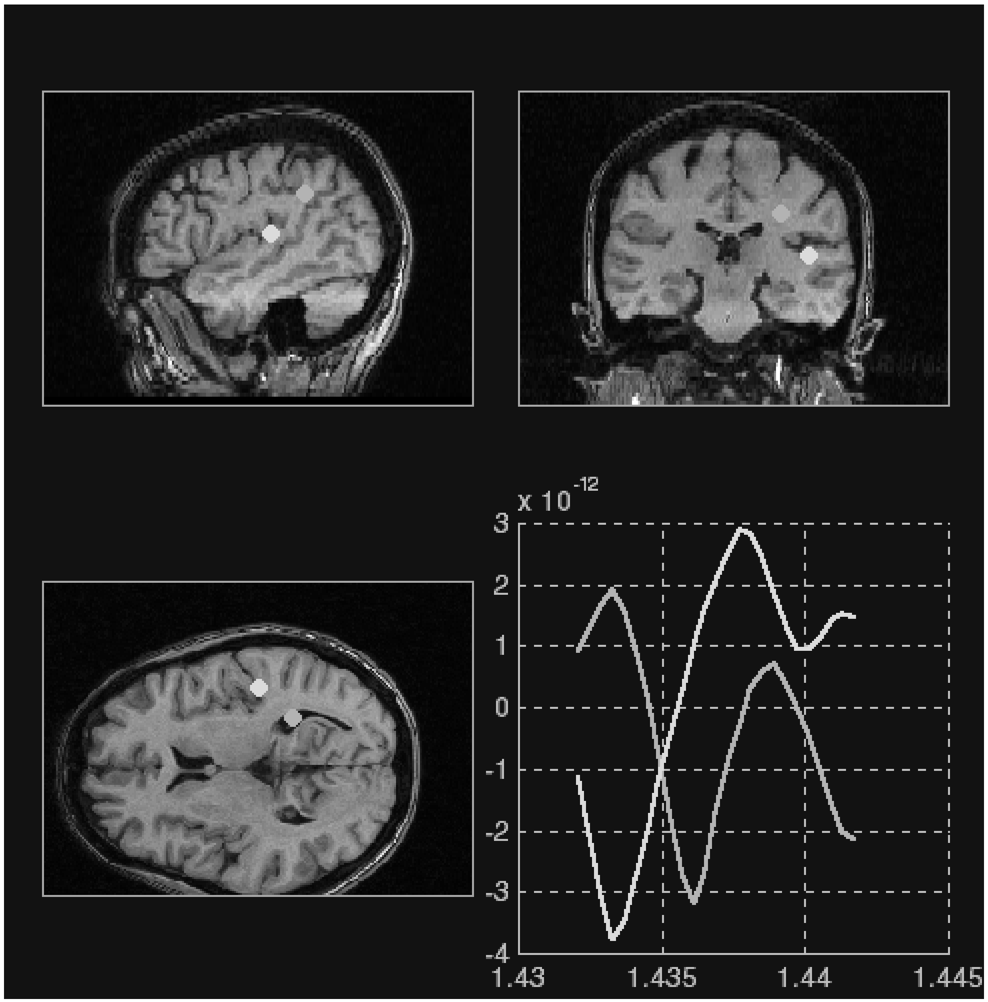
- Patient surgical candidate with temporal lobe epilepsy
- MEG data acquired continuously for five minutes
- Data manually scanned for interictal spike activity and extracted as one second data segments

Interictal Spike Processing

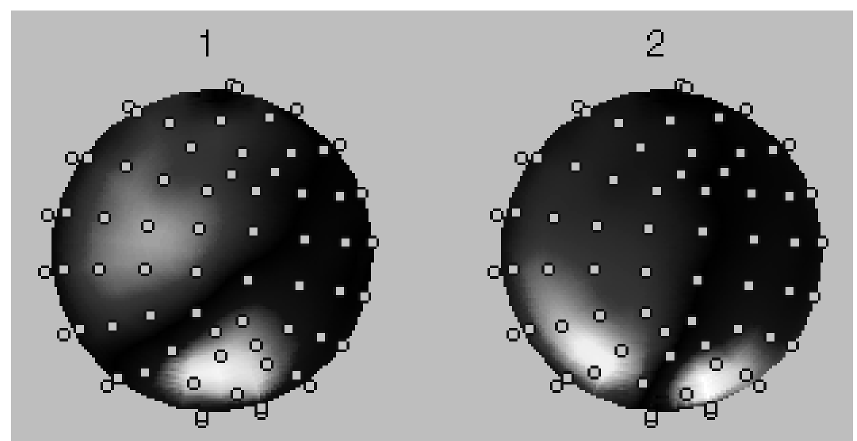


BrainStorm

Spike Activity Results



- Two locations adjacent, in unsuspected parietal region.
- Confirmed with depth electrode.



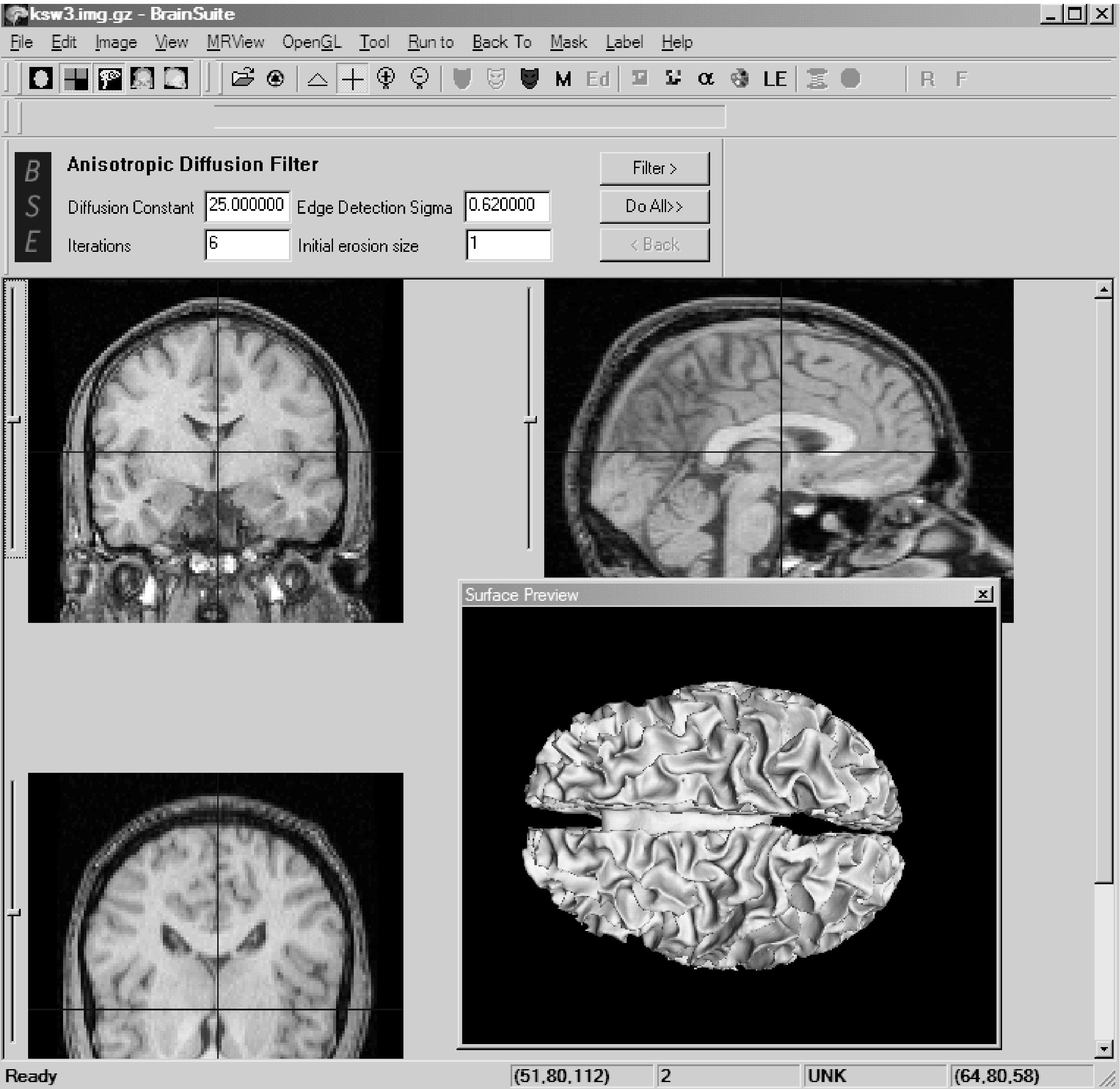
BrainStorm

Research Software

- "OEM" software supplied with the commercial EEG and MEG instruments.
- Third-party (BESA, BrainVoyager, EMSI, ASA, Curry).
- Research software from collaborators:
  - University of Southern California/CNRS
  - Los Alamos Biophysics Group
  - MGH-NMR

USC BrainStorm

- Matlab research software combining parametric and imaging solutions into a visualization suite.
- http://neuroimage.usc.edu



BrainSuite

- Surface extraction, with bias field and topological corrections.
- ~Automated scalp, skull, cortex tesselations
  - Started at USC by David Shattuck, now at UCLA-LONI program (Art Toga).

Summary

- Linear imaging
  - Too many parameters for modeling; rather, transforms
  - Too few underlying data parameters for imaging
- Dipolar (multipolar) models
  - A few parameters for hypothesis testing
  - Represent regional sources
- Cortical remapping allow physiological interpretation of parametric fits.
- SEE: http://neuroimage.usc.edu
  - Publications
  - BrainStorm software
  - BrainSuite for surface extraction, tesselation
  - Phantom Data

Other Topics

- Preprocessing – artefact rejection
- Array calibration – perturbation studies
  - Phantom studies
- Cramer-Rao theoretical error, Monte Carlos, Bootstrapping.
- Colored noise handling
  - “Pre-whitening” demands accuracy
  - Necessary for gradiometers with magnetometers, combined EEG & MEG
  - “sources not of interest”